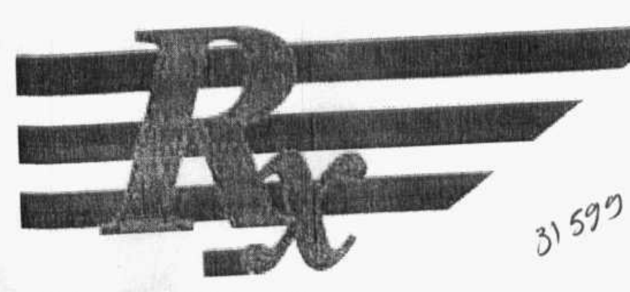




PHARMACOLOGY AND THERAPEUTICS

FOR
"VETERINARY MEDICAL STUDENTS"

VOLUME II
(ENDOCRINE PHARMACOLOGY,
CHEMOTHERAY,
DRUG TOXICOLOGY,
& CLINICAL PHARMACOLOGY)

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1st edition

PREFACE

Our chief objective is to provide students of Veterinary Medicine with a concise but comprehensive source of Pharmacology which is a very rapidly progressing science in both human and animal fields. The book is written in simple English so that it may be understood as easy as possible. It is also supported by figures, tables and illustrations whenever possible to assist students to utilize and remember pharmacological information provided.

The book is presented in two volumes; Volume I which includes General and Systemic Pharmacology; and Volume II which includes Endocrine Pharmacology, Chemotherapy, Drug Toxicology and Clinical Pharmacology. In addition, laboratory notes "Volume III" on Experimental Pharmacology & "Volume IV" on Dispensing are also available to help students in memorizing, analyzing and reporting data of their experiments along the practical course of Pharmacology.

We hope our simple book gets acceptance by its readers and any suggestions are highly encouraged and will be highly appreciated.

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XI. ENDOCRINE PHARMACOLOGY

- **Definitions and Classification**
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BY: ABUBAKR M. EL-MAHMOUDY, PhD

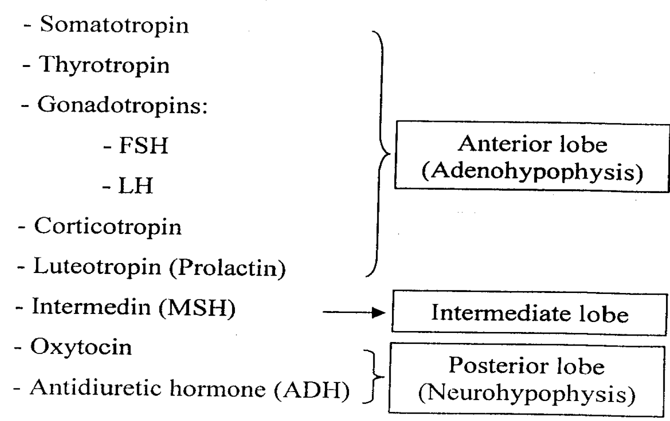
Def.: Endocrine pharmacology is the study of hormones' pharmacology. A hormone is a chemical substance secreted by an endocrine gland and transported by the blood to distant sites in the body where it produces its action.

Classification:

Hormones are classified in different ways, importantly are the followings:

I- According to the secreting gland into:

1- Pitutary hormones:



2- Hypothalamic hormones comprise releasing hormones (RHs) & inhibitory hormones (IHs):

- Somatotropin RH
- Thyrotropin RH
- Gonadotropin RHs
- Corticotropin RH
- Luteotropin IH

3- Thyroid hormones:

- Thyroxine (T4)
- Tri-iodothyronine (T3)
- Calcitonin

4- Parathyroid hormones:

- Parathormone

5- Adrenocortical hormones:

- Mineralocorticoids (Aldosterone & desoxycorticosterone)
- Glucocorticoids (Cortisone & cortisol)
- Sex hormones (Androgens, Estrogens & progestogens)

6- Adrenomedullary hormones

- Nor-epinephrine & Epinephrine

7- Pancreatic hormones

- Insulin
- Glucagon

8- Gonadal hormones

- Androgens (Testes)
- Estrogens (Ovary)
- Progestogens (Corpus luteum/placenta)

II- According to the <u>chemical nature</u> of the hormone into:

1- Steroidal hormones

- Adrenocortical hormones (mineralocorticoids, glucocorticoids & sex hormones)

2- Non-steroidal hormones

- **Polypeptides & proteins:**
  - Pitutary
  - Pancreatic
  - Parathormone
  - Calcitonin
- **Amino acid derivatives (Tyrosine derivatives):**
  - T3 and T4
  - Catecholamines

III- According to the <u>physical nature</u> of the hormone into:

1- Fat soluble:

- Steroidal hormones
- T3 and T4

2- Non-fat soluble

- All non-steroidal hormones except T3 and T4

IV- According to the <u>main action</u> of the hormone into:

A. **Pituitary hormones** (of variable actions on growth, metabolism and reproduction).

B. **Hormones affecting metabolism:**

- Glucocorticoids
- Mineralocorticoids
- Thyroid hormones

- Parathyroid hormone
- Pancreatic hormones

C. **Hormones affecting reproduction**:
- Androgens
- Estrogens
- Progestogens
- Oxytocin
- Gonadotropins

General mode of action of hormones

Hormones act via their specific receptors which are classified into:

1- Extracellular (membrane) receptors:

- Internalized membrane receptors as those of insulin
- Fixed membrane-bound receptors as those of non-steroidal hormones (Nonfat-soluble) except T3 and T4 (fat-soluble).

2- Intracellular receptors:

- Cytoplasmic receptors (free) as those of steroidal hormones and those of T3 & T4. The hormone-receptor complex then stimulates
- Nuclear receptors, which start transcription of certain mRNAs and protein synthesis.

P.S. Hormones acting via intracellular receptors should be fat-soluble hormones to pass through lipoid cell membranes.

Some hormones act via changing membrane permeability as ADH and insulin.

I- PITUITARY HORMONES

- All pituitary hormones are polypeptides.
- They are not effective orally.
- Act by activating fixed membrane-bound receptors

I-1. Somatotropin
(Growth hormone)

Control: its release is controlled mainly by SRH.

Actions:

1- Anabolic, increases growth of soft tissues & bones.

2- Over-production leads to "gigantism (before closure of epiphyseal ends) or acromegaly (after closure of epiphyseal ends)" while under-production leads to "dwarfism".

3- It has anti-insulin actions:

a. Carbohydrates → hyperglycemia.

b. Fat → lipolysis → lipaemia.

Uses:

Limited but may be used in "dwarfism" of human only by i.v. route

I-2. Thyrotropin

Control: its release is controlled by TRH.

Actions:

- It ↑ vascularity, and thus the size and activity of thyroid gland.
- Increased thyroid activity involves:
    - uptake of iodide.
    - proteolysis of thyroglobulin.
    - production & release of T3 and T4.

Uses:

- Hypothyroidism.
- Acanthosis nigricans in dogs.
- Diagnosis of thyroid dysfunction.

I-3. Corticotropin

(Adrenocorticotropic hormone; ACTH)

Control: ACTH is released under the effect of corticotropin-RH in:

- Emotional conditions
- Stress
- Decreased level of adrenocortical hormones (Addisons's disease).

Actions:

- Increases vascularity and thus the size & activity of adrenal cortex.
- Increases level of mineralocorticoids
- Increases level of glucocorticoids
- Increases level of adrenal sex hormones

Uses:

- Diagnosis of Addison's disease (Adrenal cortex dysfunction)
- Facilitates withdrawal of cortisone.

I-4. Pituitary Gonadotropins

They include follicle stimulating hormone (FSH) and luteinizing hormone (LH). They are released under the control of gonadotropin releasing hormones (GnRH).

Pituitary gonadotropins can be summarized in the following table:

	FSH (Follicle stimulating hormone; Human menopausal gonadotropin)	**LH (Luteinizing hormone; Interstitial cell stimulating hormone; ICSH)**
Actions	- Development of ovarian follicles (♀) - Spermatogenesis (♂) - Synthesis & release of estradiol (♀) - Puberty (♀).	- Maturation of ovarian follicles (♀) - Ovulation (♀) - Maintenance of CL & synthesis and release of progesterone (♀) - Synthesis & release of testosterone (♂) - Puberty (♂)
Uses	Infertility due to hypothalamo-hypophyseal lesion (♂ & ♀) - Delayed puberty in ♀ - ↑# of twins (♀) - Estrus Synchronization (♀) - Oligospermia (♂)	- Infertility due to hypothalamo-hypophyseal lesion (♂ & ♀) - Delayed puberty in ♂ - Anovulatory estrus (♀) - Cryptorchidism (♂) - Decreased libido (♂)

P.S. Please refer also to non-pituitary gonadotropins in the section of hormones affecting reproduction.

I-5. Luteotropin

(Luteotropic hormone; LTH; lactogenic hormone; prolactin)

Actions:

- It is responsible for lactation by ↑ vascularity and thus size & activity of mammary gland.

Control:

- Its release is controlled mainly by LIH of hypothalamus.
- LIH is found to be "Dopamine"; therefore in hypothalamic lesions associated with dopamine decrement, the level of prolactin increases leading to ↑ milk secretion (galactorhea) and stopping of menopausal cycle (amenorrhea) due to ↓ FSH & LH on the basis of feed back mechanism.
- Similarly, drugs that ↓ dopamine action (dopamine antagonists) also may lead galactorhea & parkinsonin including:
    1- Metoclopramide, Chlorpromazine & Haloperidal (dopamine receptor blockers)
    2- Reserpine (depletor of dopamine stores)
    3- Alphamethyldopa (inhibitor of dopamine synthesis)
    4- Cimetidine, ranitidine, ...(H_2 receptor blockers)

The condition can be corrected by dopamine agonists as L-Dopa and Bromocryptine (Parlodel®, Lactodel®). On the other hand, dopamine antagonists are useful in treatment of agalactia.

I-6. Intermedin

(Melanocyte stimulating hormone; MSH)

This hormone is of less importance in mammals but acts on melanocytes in amphibia & reptiles; increasing & maintaining their skin color.

I-7 Antidiuretic hormone
(ADH; Vasopressin)

- **Def.:** A polypeptide hormone of posterior pituitary acting on distal convoluted tubules and collecting ducts to reabsorb more water and thus decreases urine volume.

- **Synthesis & Release control:**

1. ADH is formed in the cell bodies of para-ventricular and supra-optic nuclei, then migrate through the axons to the perivascular nerve endings; where it is stored in neurosecretory granules in the posterior lobe of pituitary combined with a carrier protein.
2. Ca^{++} influx occurring upon coming of an action potential, frees ADH from the protein, and then it is exocytosed into the blood stream.
3. ADH is released by:
   - Stimulation of osmoreceptors in hypothalamus during hyperosmosis of the blood.
   - Stimulation of volume receptors in left atrium and pulmonary veins during hypovolemia (hemorrhage).
   - Some drugs as morphine, barbiturates, ...etc

Actions:

1- On the kidney: it ↑ permeability of distal convoluted tubules and collecting ducts to reabsorb more water. Deficiency of ADH, thus, leads to diabetes insipidus.

2- On CVS: it causes vasoconstriction in larger doses, (hence the name vasopressin) of all blood vessels especially capillaries and venuoles increasing blood pressure.

3- On smooth muscles: it contracts smooth muscle of GIT and uterus.

4- On pituitary: it increases secretion of ACTH.

Uses:

ADH is destroyed by gastric enzymes as trypsin so it is not effective orally, however, it can be used as oily preparation using i.m. route in the following:

- Diabetes insipidus
- Hypotension
- Intestinal paresis and distension
- Calf scour to compensate the excessive loss of fluids and guard against cardiac arrest that may follow hemoconcentration.

I-8. Oxytocin

Def.: It is a polypeptide hormone of posterior pituitary. It could be also supplied as synthetic preparation "syntocinon®".

Release: It is the hormone of parturition; its secretion is markedly increased at the end of pregnancy.

Actions:

- It contracts uterine muscle after its sensitization with small dose of estrogen.
- It relaxes the cervix and dissociates pelvic symphesis.
- It contracts myoepithelial cells of mammary gland inducing let down of milk.
- After sexual intercourse, it helps ascending of sperms by inducing upward contractile waves in the female genital tract.

Mode of action:

The direct action of oxytocin on myometral and myoepithelial cells is achieved via binding of oxytocin with specific receptors. The expression of these receptors increases shortly before parturition in both uterus and mammary gland. The expression decreases again in uterine cells after

delivery, but continues in mammary gland for up to 2 years to help let down of milk.

Uses:

- uterine inertia, when fetal position is normal and cervix is dilated.
- retained placenta.
- postpartum hemorrhage (and uterine bleeding in general).
- uterine prolapse.
- agalactia

II- HORMONES AFFECTING METABOLISM

II-1 Glucocorticoids (cortisol)

Def., source & control:

- These are steroid hormones secreted from *zona fasiculata* of suprarenal gland.
- They are secreted under the effect of corticotropin.

Actions:

1. Negative feed back effect on corticotropin by antagonizing corticotropin-RH from hypothalamus.
2. Carbohydrate metabolism:

Glucocorticoids produce hyperglycemia via:

- ↑ neoglucogenesis.
- ↓ glucose utilization by peripheral tissues and ↓ its sensitivity to insulin.

3. Protein metabolism:

- Glucocorticoids are <u>catabolic</u> on most of tissues except on the liver & visceral organs.
- They mobilize amino acids from proteins, which will then uptaken by liver converting them into carbohydrates & urea.

4. Fat metabolism:

- Lipolysis, increasing level of free fatty acids in the blood (lipaemia).
- Redistribution of fat depots in fascio-cervical and trunkal areas leading to what is called "moon face & "buffalo hump".

5. Anti-inflammatory, anti-allergic & antirheumatic effects by:

↓ phospholipase enzyme → ↓ arachidonic acid → ↓ PGs.

↓ migration of inflammatory cells to site of inflammation.

↓ capillary permeability → ↓ edema.

↑ stabilization of lysosomes and mast cells.

6. GIT

- Long-term use leads to ↓ gastric mucous and may be gastric ulcer.
- Anti vit. D: it ↓ Ca^{++} absorption from intestine → hypocalcemia

7. C.V.S.

- Hypervolemia due to Na^+ and H_2O retention.
- ↓ uptake of noradrenaline leading to vasoconstriction.
- Both hypervolemia and noradrenaline lead to hypertension.
- ↑ platelets, hastening blood coagulation (with risk of thrombosis).
- Lymphopenia, eosinopenia & ↓ antibody formation due to its catabolic effect on lymphoid tissue.

8. Delayed wound healing due to its catabolic effect on fibroblasts and decreased synthesis of hyaluronic acid.

9. Uricosuric effect.

10. Electrolytes: Na^+, Cl^- & H_2O retention and K^+ depletion.

Uses:

- Adisson's disease "Adrenocortical insufficiency".
- Inflammatory conditions:
  - Rheumatism.
  - Arthritis.
  - Sever uretric colic.
- Allergic conditions as in skin & eye allergies and in bronchial asthma.
- Anaphylactic shock.
- Organ transplantation as suppressive for antibody formation.
- Autoimmune diseases.

Contraindications:

1. Cushing's syndrome.
2. Diabetes mellitus
3. Hypertension.
4. Peptic ulcer
5. Thromboembolic diseases.
6. Digitalin therapy
7. Pregnancy (as it causes teratogenicity & growth retardation)

8. Abrupt withdrawal (as this may lead to Addison's disease)

Precautions:

1. Repeated test for glucose in urine.
2. Repeated test of blood pressure.
3. Diet should contain much protein, Ca^{++} & K^{+}, less carbohydrate & NaCl & normal fat.
4. Gradual withdrawal.

Preparations of glucocorticoids:

1. Cortisone (in-active) $\xrightarrow[\text{Liver}]{\text{H}}$ hydrocortisone (cortisol; active)
2. Prednisone:

   Synthetic preparation as cortisone, so it must be given <u>only orally</u> to be activated in the liver during its first pass effect.
3. Prednisolone:

   Stnthetic preparation as cortisol so it can be used orally as well as by I.M., I.V., and intra-articular routes.
4. Beclomethasone: given by inhalation in resistant bronchial asthma
5. Betamethasone & dexamethasone: are flourinated cortisols.
6. Triamcinolone is a cortisol derivative.

II- 2- Mineralocorticoids

(Aldosterone & Desoxycorticosterone)

Def., source & control:

- Steroid hormones of *zona glomerulosa* of suprarenal gland
- Secreted under the effect of:

• Renin-angiotensin system → angiotensin II → ↑ aldosterone synthesis in response to ↓ G.F.R and ↓ blood volume (hypovolemia)

• ↓ Na^+, ↑ K^+ in blood → ↑ only aldosterone release by direct effect.

Mode of action: Aldosterone stimulates its specific intracellular cytoplasmic receptors stimulating synthesis of "permease" which is the carrier protein responsible for the active re-absorption of Na^+ in the distal convoluted tubules.

Actions:

1- Kidney:

- In the distal convoluted tubules, it causes:
  - Na^+, Cl^- & H_2O retention
  - K^+, H^+, Mg^{+2} & NH_4 depletion
- Its action is potentiated by glucocorticoids.
- Its action is ↓ by progesterone (competitive antagonism)
- Escape phenomenon:

Prolonged hypervolemia or primary hyperaldosteronism leads to decreased sensitivity of the distal convoluted tubules to aldosterone → no permease synthesis → no Na^+ & H_2O retention and by rule K^+ is still excreted with the following findings:

- hyponatremia
- hypopotassemia (due to potassium depletion)
- alkalosis (due to hydrogen depletion more than NH_4)
- hypertension (present by rule due to hypervolemia)

2- GIT, salivary & sweat glands:

As kidney but weaker, of delayed onset, and there is no escape phenomenon.

The actions of desoxycorticosterone is as that of aldosterone but weaker (1/30 of its potency).

Both mineralocorticoids are ineffective orally.

Uses:

- Rarely used therapeutics but may be tried in hypotension
- Aldosterone-antagonists as "Spironolactone" act as diuretics.

Preparations:

- Deoxy cortone acetate (Corterone) = 1/40 as aldosterone
- Desoxy corticosterone acetate (DOCA) =1/30 as aldosterone
- Fludrocortisone acetate (Flurocortisol) has a strong mineralocorticoid action (125 times as aldosterone) and a strong glucocorticoid action (10 times as cortisol) and the only corticoid that can be given orally.

II-3 Thyroid hormones

(Thyroxine "T4", Tri-iodothyronine "T3" & Thyrocalcitonin)

II-3-1: T3 & T4

Def., source & control:

- Amine hormones secreted under control of thyrotropin from thyroid gland follicular cells. Thyrotropin enhances the function of thyroid cells by increasing its vascularity for active uptake of inorganic iodide (about 50% circulatory iodide is used by thyroid).
- Trapped iodide combines with the "tyrosyl residue" which is synthesized by thyroid cells then stored in the follicular colloid. Iodination process is completed in 4 steps:

Tyrosyl residue + I → Mono-iodo-tyrosine

Mono-iodo-tyrosine + I → Di-iodo-tyrosine

Di-iodo-tyrosine + I → Tri-iodo-thyronine (T3; more potent)

Tri-iodo-thyronine + I → Tetra-iodo-thyronine (T4; Thyroxine; less potent)

- By synthesis and release of T3 and T4, the action of thyrotropin is stopped by feed back mechanism. However, in case of iodide deficiency, the enhancement effect of thyrotropin on thyroid cells continues but in vain leading to thyroid enlargement "goiter".

Mode of action of T3 & T4:

Thyroid hormones activate specific nuclear receptors increasing transcription and production of almost all metabolic intracellular enzymes.

Actions:

1- Negative feed back mechanism with thyrotropin.
2- Increase basal metabolic rate (BMR) by increasing intracellular metabolic enzymes and increasing the size and number of mitochondriae.
3- Carbohydrate metabolism:

- Enhancement of absorption of glucose from intestinal tract leading to initial hyperglycemia followed by hypoglycemia due to rapid utilization of glucose by tissues and active metabolic enzymes.
- Glycogenolysis

4- Protein metabolism:

T3 & T4 are catabolic hormones, they elevate the level of free amino acids in the blood.

5- Fat metabolism:

T3 & T4 are lipolytic hormones, they elevate the level of free fatty acids in the blood.

6- Cholesterol: T3 & T4 lead to hypocholesterolemia due to the consumption of cholesterol in synthesis of bile acids.

7- Energy metabolism: T3 & T4 have calorigenic or thermogenic effect by increasing oxidative phosphorylation processes.

8- T3 & T4 increase O_2 consumption and CO_2 production.

9- Kidney: T3 & T4 have diuretic effect, they increase urinary excretion of Ca^{++}, Na^{+} & H_2O.

10- CVS:

- T3 & T4 have direct myocardial stimulant action producing tachycardia.
- T3 & T4 have sensitization effect on blood vessels for the action of sympathomimetics producing vasoconstriction.
- The previous two effects on CVS lead to hypertension.

11- T3 & T4 enhance mobilization of Ca++ from bone into the blood leading to hypercalcaemia and thus hypercalciuria.

12- Growth:

- T3 & T4 increase physical growth, mental development and sexual maturation.
- Hypothyroidism lead to "critinism" (stunted growth) in youngs; and "myxedema" (lethargy and intolerance to cold) in adults.
- Hyperthyroidism doesn't lead to overgrowth as in case of increased level of pituitary growth hormone, but to sever loss of weight due to increased catabolism.

Uses:

1- To increase milk production "with extra food".
2- To increase fertility in sluggish bulls.
3- To increase growth rate in youngs.
4- To increase egg laying in poultry.
5- Obesity.
6- Hypercholesterolaemia.
7- Hypothyroidism.
8- Amenorrhea.
9- Goiter

Table (17): Pharmacological differences between T3 and T4

	T4	T3
Onset	Delayed	Rapid
Duration	Long	Short
Potency	Less potent	More potent
Bioavailability	65%	95%

Anti-thyroid drugs

Def.: these are the drugs which prevent the synthesis and peripheral actions of thyroid hormones.

Members:

Anti-thyroid drugs are classified according to their mode of action into the following 3 groups:

1- **Drugs which inhibit iodide trapping:**
   This group is sub-classified into three groups according to mechanism of inhibiting iodine trapping as follows:
   a. Perchlorate$^-$, Thiocyanate$^-$ & Nitrate$^-$ which are monovalent chemical groups that compete with iodide.
   b. "Di-nitro-phenol" which inhibit ATP synthesis producing cellular disability.
   c. "Ouabain" which is an ATPase inhibitor prevents cells from utilization of ATP leading also to cellular disability.
2- **Drugs which inhibit iodination process and thus prevent synthesis of T3 & T4.** This group includes members of "Thioamides" (Thiouracils or thioureas) such as Thiouracil, Propyl-thiouracil, Methyl-thiouracil, Thiourea, Carbemazole and Methimazol.
3- **Drugs which destroy thyroid tissue** as the radioactive I^{131}. This is trapped by thyroid cells, producing radioactive T3 & T4 which while their storage inside thyroid follicles they emit beta and gamma rays which are destructive for follicular cells.

Uses:

1- Hyperthyroidism
2- Cancer thyroid
3- Testing function of thyroid (using I^{132})

II-3-2: Thyro-Calcitonin (Calcitonin)

Def., source & control:

- Calcitonin is a polypeptide hormone which is not effective orally.
- It is synthesized and released by parafollicular cells (C-cells) of thyroid in response to hypercalcaemia.

Mode of action: Calcitonin acts via activation of specific membrane-bound receptors.

Actions:

- It is a hypoclcaemic hormone.
- It decreases bone resorption (mobilization of Ca^{++} from bone to the blood).
- It decreases Ca^{++} reabsorption (i.e from renal tubules). However, it has no effect on Ca^{++} absorption from intestine.

Uses:

- Hypercalcaemia
- Paget's disease of bone.
- Post-menopausal osteoperosis together with or without estrogen.
- Hyperparathyroidism.
- Vit. D poisoning.

Preparations:

Although Calcitonin is in-effective orally, yet, "Bisphosphanate" members as "Alendronate" (Fosamax)® is a calcitonin analogue with advantage of oral effectiveness.

II-4 Parathyroid hormone
(Parathormone)

Def., source & control:

- Parathormone is a polypeptide hormone which is not effective orally.
- It is synthesized and released by parathyroid gland cells in response to hypocalcaemia.
- Low blood Mg^{++} level decrease parathormone release.
- Blood phosphate has no direct effect; however high blood phosphate level inhibits active bone resorption → decrease Ca^{++} blood level → enhance parathormone release.

Mode of action: Parathormone acts via activation of specific membrane-bound receptors.

Actions:

- It is a hyperclcaemic hormone; it increases blood Ca^{++} by:
    - It increases bone resorption through:
        - increasing osteoclastic activity.
        - increasing lysosomal activity.
        - increasing glycogenolysis with production of lactic acid which solubilizes exchangeable Ca^{++}.
    - It increases Ca^{++} & decreases phosphate reabsorption from proximal convoluted tubules.
    - It increases Ca^{++} absorption from intestine (unlike calcitonin).
    - It increases renal hydroxylation of Vit. D3 (Cholecalciferol) into 1,25-dihydroxy-cholecalciferol.

Uses:

- Hypocalcaemia.
- Hypoparathyroidism.

Preparations:

Although Parathormone is effective by i.m. injection yet, its use may lead to antibody formation.

"Dihydrotachysterol" is a relatively new drug with similar effects to both parathormone and Vit. D; so it is very effective in managing hypocalcaemic states.

II-5 Insulin

Def.: it is a polypeptide hormone of 51 amino acids arranged in two chains, chain A (21 amino acids) and chain B (30 amino acids). The two chains are connected by two S-S bridges which are essential for insulin action.

Synthesis & storage:

- Insulin is produced by β-cells of islets of Langerhans in pancreas. Pancreas contains about one million islets.
- Synthesized insulin inside the body is stored in granules inside β-cells until its release.
- Now, insulin is completely synthesized in the lab after cognition of amino acid sequence involved in its structure.

Release:

Granular insulin is released from β-cells by the following:

- Foods as: glucose, fructose, mannose, arginine and phenylalanine. Intravenous glucose administration leads to sharp rise in insulin blood level.
- Hormones:
    - Gastrointestinal hormones as secretin, gastrin and cholecystokinin.
    - Systemic hormones as growth hormone, T3 & T4.
- Autonomic drugs including:
    - β -agonists
    - α-antagonists
    - M-agonists
- Other drugs as sulfonylureas

Fate:

Insulin is a hormone of short half-life.

It is completely uptaken by most of tissues and [illegible] by "Insulinase" (Glutathione-insulin transhydrogenase).

Insulin, therefore, doesn't appear in the urine.

Mode of action:

Insulin acts via activation of membrane receptors which are then internalized increasing intracellular cAMP.

Actions:

- Carbohydrate metabolism: insulin has a hypoglycemic action via:
  - Facilitation of glucose entry into the cells as fat cells and skeletal muscle cells; but not liver, brain adrenal medulla, WBCs and RBCs as they have their specific glucose transporters (GLUT).
  - Activation of hexokinase (glucokinase) which initiates glucose utilization
  - Increasing glycogenesis by activation of glycogen synthetase enzyme
  - Inhibition of glycogenolysis and neoglucogenesis.

- On lipid metabolism:
  - Stimulates lipogenesis
  - Inhibits lipolysis
  - Decreases plasma free fatty acids
  - Decreases ketone body formation by the liver
- On protein metabolism: insulin is anabolic hormone as:
  - It increases amino acid uptake by the cells for protein synthesis.

- It decreases nitrogen (urea and ammonia) in the urine [+ve nitrogen balance]
- It augments the action of growth hormone.

◙ Insulin increases uptake of K^+, Mg^{++} and phosphate to be used as co-enzymes for glucose utilization reactions; so their levels are decreased in the blood.

Kinetics, sources and preparations of insulin:

- Insulin is not effective orally due to digestion by proteolytic enzymes.
- Used parenterally, usually by s.c. and in emergency soluble preparations of insulin can be given intravenously.
- Of short half life; 40 minutes after s.c. administration and 5 minutes after i.v. administration.
- Insulin extracted from bovine pancreas has 3 amino acids different from those of human insulin. While porcine insulin has only one different amino acid, so it is less antigenic than that of bovine; however both were used successfully.
- Humanized insulin is that of bovine or porcine but the different amino acids were corrected using genetic techniques.
- Human insulin is that insulin extracted from human pancreas and nowadays it could be produced on large scale using recombinant DNA technology.
- Different preparations of insulin including soluble solutions and insoluble suspensions either short acting, intermediate acting or long acting are now produced synthetically.

Factors modifying insulin action:

- Muscular exercise; it enhances glucose oxidation and lower doses of insulin are then required.

- Insulin antibodies; persons receiving large doses (more than 200 units daily) of antigenically different insulin may develop antibodies which may require changing type of insulin used.
- Food regimen
- Concurrently administered drugs.

Uses:

- Diabetes mellitus.
- To increase appetite and body weight.

Oral Anti-diabetics

"Synthetic hypoglycemic agents"

Def.: These are the drugs which decrease blood glucose level and can be given orally, unlike insulin.

Members: They include the following groups:

1- **Sulfonylureas:**

1st generation:

Tolbutamide (Rastinon)®

Chlorpropamide (Diohenase)®

2nd generation:

Glibenclamide (Daonil)®

Glipizide (Minidiab)®

Gliclazide (Diamicron)®

Glimepride (Amaryl)®

Mode of action: All sulfonylureas decrease blood sugar level by the following mechanisms:

- They block ATP-sensitive K^+ channels of β-cells leading to membrane depolarization and release of insulin.
- They decrease catecholamine release

- They decrease glucagon release
- They increase number and sensitivity of insulin receptors in peripheral tissues.

2- Biguanides:

Metformin (Glucophage®, Cidophage®)

Phenformin (Insoral®)

Mode of action: All biguanides don't affect beta-cells but they decrease blood sugar level by the following mechanisms:

- They enhance glucose uptake by skeletal muscles.
- They decrease neoglucogenesis.
- They inhibit glucagon release.

Uses of oral antidiabetics:

- Mild degrees of diabetes mellitus especially non-insulin dependent type (diabetes type II).
- Sulfonylureas can be used, in addition, in insulin dependent type of diabetes (Diabetes type I).
- Biguanides has anorxiogenic effect so they can be used in decreasing overweight. On the other hand, sulfonylureas increase appetite so they should be avoided in obese patients.

P.S. Phenformin is now obsolete as it causes lactic acidosis, while metformin and sulfonylureas are widely used.

II-6- Glucagon

Def., source and control:

- Glucagon is a single chain polypeptide hormone secreted by α-cells of pancreatic islets of Langerhans.
- It is released in response to hypoglycemia.

Actions:

- Enhances glycogenolysis by stimulating liver phosphorylase and release of catecholamines.
- Enhances neoglucogenesis
- Enhances lipolysis and thus increases blood free fatty acids
- Stimulates myocardium.

Uses:

- Hypoglycemia

Glucogenic agents

Def.: These are the drugs which increase blood glucose level and stimulate formation of glucose from proteins.

Members:

Glucogenics include the following:

- Dextrose itself
- Glycerol
- Propylene glycol
- Sodium propionate
- Glucocorticoids

Uses:

- Hypoglycemia

III- HORMONES AFFECTING REPRODUCTION

III-1. Gonadotropins

- **Gonadotropins are either:**
  - Pituitary gonadotropins including FSH (follicle stimulating hormone) and LH (lutenizing hormone); discussed earlier.
  - Non-pitutary gonadotropins with more or less similar functions could be secreted from other tissues as placenta including PMS (pregnant mare serum) and HCG (human chorionic gonadotrophin).

Gonadotrophins are responsible for maintaining the function of testes and ovary and regulating the female sexual cycle.

FSH:

- Development of Graffian follicles in the ovary.
- Stimulates estrogen secretion by follicles (puberty in females).
- Development of spermatogonia in the testes (fertility in males).

LH:

- It induces ovulation and luteinization (fertility in females).
- It activates Leydig cells to secrete testosterone (puberty in males).

HCG (Prolan):

- It is produced by placenta of pregnant women.
- It is a main source of LH.
- It appears in the urine and thus provides the basis of pregnancy tests as Friedman's test.

PMS (Prolan A):

- It appears in the serum of pregnant mares during the time period between 45^{th} and 90^{th} days of pregnancy.
- It is a main source of FSH.

GnRH (Gonadotropin releasing hormone; Gonadorelin; Receptal®):

- It is synthetic non-antigenic decapeptide.
- It stimulates release of endogenous gonadotropins (if pituitary gland is normal) in physiological amounts inducing ovulation and lutenization.

Therapeutic uses of gonadotropins & GnRH:

As those of pituitary gonadotropins

III-2. Sex hormones

- Sex hormones are chemical steroids containing “pentanophenantherine ring” that is the basic ring of steroids.
- They include androgens, estrogens and progestogens.

III-2.1. Androgens

Def., source & control:

- These are the male sex hormones which are responsible for development of male genital organs and appearance of male sexual characters.
- The main androgen is testosterone; it is synthesized in the testes, released under LH control; and then converted to its active metabolite "dihydro-testosterone" by 5- α-reductase enzyme in most tissues except skeletal muscle and bone marrow which have different pathway. Absence of 5-α-reductase leads to pseudohermaphroditism which is characterized by male hypogonadism but well-developed skeletal muscle. The case could be treated by dihydrotestosterone. Deficiency of testosterone receptors leads to feminization which has no medical treatment.
- "Androsterone" is a derivative of testosterone of weaker potency formed in the adrenal cortex, released under ACTH control and excreted in urine.
- Natural testosterone is supplied but it is not effective orally due to extensive hepatic first pass metabolism; so are supplied as s.c implants.
- Semi-synthetic testosterones have been supplied as "fluoxymesterone" which is a potent oral androgen.
- Synthetic testosterones have been also developed as testosterone propionate (i.m and sublingual), methyl testosterone (sublingual and oral), norethandrolene, trienbolone. ...etc.

Actions:

There are two types of androgenic actions; virilizing (musculizing) actions and anabolic actions:

A- Virilizing actions:

- Maintenance of spermatogenesis
- Development of male accessory sexual organs including epididymis, ductus deferens, ...etc.
- Development of male sexual characters including male body conformation, stronger lower voice, hair growth, ...etc
- Maintenance of libido

B- Anabolic actions:

- Nitrogen retention.
- Protein sparing and deposition.
- Decrement of de-amination processes.
- Electrolyte retention (with side effect of edema).
- Increasing appetite and food conversion.

Therapeutic uses of androgens:

- Male hypogonadism as sexual impotency, decreased libido and delayed puberty.
- Retention of testes (cryptorchidism).
- Feminization of certain animals as dogs.
- Mammary tumors as in bitches.
- Estrous suppression in sexually active female animals as in dogs and cats.
- Aging and debility.
- Growth promotion for its anabolic activity.

Anti-androgens

- These are the drugs which antagonize the actions of testosterone and its derivatives.
- Natural anti-androgens are exemplified by estrogen and progesterone (physiological antagonists).
- Synthetic anti-androgens are also produced as "delmadinone acetate", "cyproterone" and "flutamide" which act by competition with androgens for their receptors (competitive pharmacological antagonists).

Therapeutic uses of anti-androgens:

- Hyper-sexuality and aggressiveness in males.
- Prostate enlargement & cancer prostate.
- Corticosteroid-resistant dermatoses.
- Male baldness.
- Female hirsutism and virilization.

III-2.2. Estrogens

Def., source & control:

- These are the female sex hormones which are responsible for development of female genital organs and appearance of female sexual characters.
- The main natural powerful estrogen is "Estradiol". It is synthesized by Graffian follicles in the ovary and placenta under the control of FSH. Small amount is synthesized by adrenal cortex under the effect of ACTH. Estradiol is oxidized in the liver into "estrone" or hydrated into "estriol". All estrogens are then conjugated with glucuronic acid and excreted in urine. It should be noted that urine does not contain any free estrogens.
- Natural estrogen is supplied as "estradiol monobenzoate" and "estradiol valerate" (i.m.).
- Semi-synthetic estrogens are supplied as "ethinyl estradiol" which is the most effective oral estrogen.
- Synthetic preparations have been also developed as "diethyl stilbosterol" (oral and paretntral) and "hexosterol" (oral).

Actions:

There are two types of estrogenic actions; feminizing actions and anabolic actions:

A- Feminizing actions:

- Development and maintenance of female genital tract by direct stimulation of the growth of both epithelium and muscles.
- Stimulation of the growth of mammary glands by increasing the growth of the duct system and deposition of fat.

- Development of female sexual characters including female body conformation, thinner & louder voice, hair growth, behavioral & physical changes during sexual cycle, ...etc.
- Small dose of estrogen is required to sensitize the action of oxytocin on the uterus.
- Small dose of estrogen stimulate secretion of prolactin of the anterior pituitary, however, large dose inhibit lactation.
- Small dose is required for progesterone to increase the thickness of endometrium (progestational proliferation).

B- Anabolic actions:

- The anabolic action of estrogen is less than that of testosterone.
- Estrogen delays termination of growth
- Estrogen enhances appetite, food consumption and food efficiency.
- Estrogen increases nitrogen retention and protein synthesis.
- Estrogen increases fat deposition in poultry.
- Estrogen increases electrolyte retention with side effect of edema.

Therapeutic uses of estrogens:

- Silent or absent heat.
- Retained placenta and mummified fetus.
- Induction of abortion in the first days of pregnancy.
- Uterine inertia.
- Contraception.
- Enlargement of prostate.
- Growth promotion.

Anti-estrogens

- These are the drugs which antagonize the action of estrogens.

- Examples are clomiphene and tamoxifen.

Clomiphene (Clomid)®:

- It is used as anti-fertility drug to induce ovulation in women.
- It competes with estrogen for its receptors, so prevents the –ve feedback of estrogen on hypothalamic FSH- & LH-RFs increasing FSH & LH levels & inducing ovulation.
- Used for induction of ovulation only in patients with normal hypothalamo-hypophyseal function

Tamoxifen (Nolvadex)®:

- It is used as anti-cancer drug.
- It also competes with estrogen for its receptors so prevents the proliferative effect of estrogen. In rodents it has anti-implantation properties by its anti-estrogenic and anti-prostaglandin effects.
- It is used for treatment of breast cancer.

III-2.3. Progestogens (Progestins)

Def., source & control:

- These are steroidal female sex hormones.

- The natural progestogen is "progesterone" which is synthesized by corpus luteum under control of lueinizing hormone (LH), placenta and in small amounts by adrenal cortex. As a drug, it is not effective orally due to extensive first pass metabolism and has very short duration of action.

- Synthetic progestins are also produced which are resistant to hepatic metabolism, effective orally and of long duration. These synthetic progestins are either:

  - Nor-testosterone derivatives as "northidrone" & "noregestrel": They have some estrogenic and androgenic properties; therefore not used to maintain pregnancy and also they may cause verilization in female foetus. They can be used in contraception.
  - 17-hydroxy progesterone derivatives as "medroxy progesterone" & "hydroxyl progesterone". They have no estrogenic or androgenic properties; therefore safe to be used in pregnancy.

Actions:

- Preparation of the uterus for implantation of fertilized ovum by thickening uterine mucosa via activation of endometrial glands (secretory phase of progestational proliferation).
- Maintenance of pregnancy by:
  - Calming of myometrium by direct relaxant effect and decreasing its sensitivity to oxytocin.
  - Inhibiting T-lymphocytes and thus prevent rejection of the foetus.

- Preventing pregnancy by:
  - -ve feed back effect on LH inhibiting ovulation.
  - Thick cervical secretion preventing penetration of sperms
- Development of mammary gland acini.
- Heat production "thermogenic"
- Inhibits aldosterone secretion.
- It has some anti-estrogenic and anti-androgenic properties.

Mode of action:

Progestins bind to specific mobile cytoplasmic receptor, then the progestin-receptor complex activates specific nuclear receptor initiating DNA transcription, mRNA synthesis which is translated to proteins.

Therapeutic uses of progestins:

- Threatened or habitual abortion (17-hydroxy progestins).
- Synchronization of estrus.
- Suppression of undesired estrus.
- Alone or together with estrogen in contraception.
- In fattening of males to produce azospermia.
- Cancer uterus.

Anti-progestogens

These are the drugs which compete with progesterone for its specific receptor antagonizing its action such as "Mifepristone".

They are used for induction of abortion in the first trimester; single dose then followed by PgF_2-α intra-vaginal pessary.

XII. Pharmacology of metabolic diseases

- **Hypocalcaemia**
- **Hypophosphataemia**
- **Hypomagnesaemia**
- **Ketosis**

BY: ABUBAKR M. EL-MAHMOUDY, PhD

This chapter gives a small hint about most common metabolic diseases in veterinary field from the pharmacological point of view. The diseases will be studied in details in clinical medicine.

Def.: Metabolic diseases are disease conditions caused by disturbance (usually decrease) in some biochemical parameters such as calcium, phosphorus, magnesium and glucose.

Hypocalcaemia
(Milk fever; Eclampsia)

Def.: It is a metabolic disease condition characterized clinically by paresis and recumbancy & biochemically by hypocalcaemia.

Causes and occurrence:

- The direct cause is the decrease of blood Ca^{++}, which is sometimes accompanied by ↓ Mg^{++} &↓ Ph^{+}.
- The disease occurs usually around the date of parturition because the severe drain of blood Ca^{++} into colostrum & milk. The disease occurs when the animal can not compensate for this drain.
- Feeding much of cereals which are rich in phytic acid → insoluble Ca^{++} complex. In contrast, Hay & grass are good Ca^{++} sources & contain less phytic acid)

- Ca^{++} is essential for neuromuscular transmission & muscle contractility, & thus deficiency of Ca^{++} lead to paresis of muscles to a degree of recumbency.

Symptoms:

1- Dullness, depression & dis-inclination to eat.
2- Nervousness followed by recombency.
3- Delirium & coma with head turned back on the flank.
4- If hypophosphatemia is present → parturient edema of brisket & udder may be observed.
5- If hypomagnesemia is present → flattering of eye lid, hypersensitivity & tremors may be observed.
6- If hypoglycemia is present → Acetonamia.
7- Recumbency for several days may lead to degenerative damages in muscle "Downer cow syndrome".

Lines of treatment& prophylaxis:

A- Treatment is directed toward correction of Ca^{++} blood level by injection of calcium preparations such as:

- Calcium borogluconate 400 ml, 40%, i.v. followed by 400 ml, 20%, s.c. as a reservoir.
- Calcium levulinate is better than gluconate as the former is less irritant.

If phosphorous deficiency is associating, the following could be tried:

- Sodium acid phosphate 30 grams in 400 ml water, given by injection.
- Tribasic Calcium phosphate 50 grams, given orally.

If hypoglycemia is accociating, glucogenic agents should be coadministered as:

- dextrose solution, 500 ml, 20~50 % according to the case, i.v.

- corticosteroids, 50 mg/cow, given by injection

B- Prophylaxis is directed toward reserving calcium in bones not in blood by the following:

- Feeding animals on low Ca^{++}, high phosphorous diet during the dry period before parturition.
- Supplementing hay and concentrate rations with mono-sodium phosphate 1-5% of the basic ration.
- Vit. D supplementation, 10-20 units/kg. bwt.
- Dihydrotachysterol single injection before parturition.

Hypophosphataemia

Def.: It is a metabolic disease condition characterized clinically by anorexia, impaired weight gain, lameness, infertility and red urine and biochemically by hypophosphataemia.

Causes and occurrence:

- The direct cause is the decrease of blood phosphorus.
- The disease occurs usually grazing of animals on crops from phosphorus-deficient soil.
- The disease usually occurs in winter upon grazing of animals only on BARSEEM without concentrate supplementation.
- Ca^{++} is essential for energy production, and integrity of cell membranes including those of RBCs, neurons and bones.

Symptoms:

1- Dullness, depression & anorexia.
2- Lameness & lumbar pain.
3- Infertility.
4- Red urine (haemoglobinuria; due to fragility of membranes of RBCs and haemplysis).
5- Chronic hypophosphatemia may lead to rickets (in youngs) or osteaomalacia (in adults).

Lines of treatment& prophylaxis:

A- Treatment is directed toward correction of phosphorus blood level by administration of phosphorus preparations such as:

- Sodium acid phosphate 30-90 grams in 400 ml water, i.v.
- Hypophosphite preparation injection; care should be taken as it is irritant and peri-vascular leakage may lead to phelebitis.

If Ca^{++} deficiency is associating, combined Ca^{++} plus phosphorus preparation should be tried such as Tribasic Calcium phosphate, 50 grams, orally.

If lumbar pain is present (manifested by lameness and tendency to recumbency), an analgesic as diclofenac should be co-administered.

B- Prophylaxis is directed toward reserving phosphorus in the body by supplying animals with a ration source containing Ca and phosphorus at a ratio rate of 2:1 as steam bone flour.

Hypomagnesaemia
(Grass Tetany)

Def.: It is a metabolic disease condition characterized clinically by tremors, tetany and hyperthaesia and biochemically by hypomagnesaemia.

Causes and occurrence:

- The direct cause is hypomagnesaemia.
- Grazing of animals on crops cultivated in areas deficient in Mg^{++}.
- Abrupt diet change to Mg^{++}-deficient diet.
- Mg^{++} inhibits neuromuscular response and depresses CNS so its decrease leads to excitation.

Symptoms:

1- Alertness and hyperthaesia.
2- Muscle tetany and convulsions.
3- Nystigmus (star gazing position).
4- Death may occur in acute hypomagnesemia.

Lines of treatment& prophylaxis:

A- Treatment is directed toward correction of Mg^{++} blood level by administration of Mg^{++} preparations such as:

- $MgSO_4$ 25%, s.c. Avoid i.v. injection as it may lead to death.
- If Ca^{++} deficiency is associating, combined Ca^{++} plus Mg^{++} preparations should be tried such as "Cal-Bor-Mag" Or "Cal-Magose".

B- Prophylaxis is directed toward reserving Mg^{++} level in the body by inclusion of "Calcined magnesite" in the ration at the rate of 30g-90g per head daily especially in areas that is suspected to be deficient in Mg^{++}.

Ketosis

(Hypoglycemia; acetonemia; pregnancy toxemia)

Def.: It is a metabolic disease condition of highly productive animals characterized clinically by intrauterine fetal death, coma and death and biochemically by hypoglycemia, ketonaemia and ketonuria.

Causes and occurrence:

- Hypoglycemia in highly performing animals.
- High milk production in dairy cows or twinning in ewes drain all blood glucose for energy, followed by depletion of glycogen store in the liver, then the body gets the required energy from fat metabolism which results in production of ketone bodies.

Symptoms:

1- Dullness and depression.
2- Acetone odor in breath and urine.
3- Abortion and intrauterine fetal death.
4- Coma and finally death.

Lines of treatment & prophylaxis:

A- Treatment is directed toward correction of blood glucose level by administration of glucogenic agents such as:

1. Dextrose, 500 ml, 50%, i.v.
2. Sodium propionate:
   It is one of Kreb's cycle intermediates, given for four days at a rate of 240-120-60 & 60 grams in ration.
   Giving cobalt along with propionate is good for propionate utilization into succinyle coA
3. Glycerol:

It is a glycogenic substance with sweet taste given as a drench or as a feed additive

Ewe is given about 120 ml while cow given about 500 ml for 2-3 consecutive days.

4. Propylene glycol:

   It is glycerol-like substance with glycogenic effect.

   It is intermediate compound in synthesis of glycogen.

   Cow is given 300 ml twice daily while ewe is given 100 ml.

   Large amounts may cause incoordination and narcosis.

5. Glucocorticoids:

   Glucocorticoids restore plasma glucose by enhancing neoglucogenesis especially from amino acids produced by the catabolic effect of cortisone on protein leading to negative nitrogen balance.

   Glucocorticoids increase liver glycogen.

   Cow is given 50 mg while ewe is given 10 mg.

XIII. Pharmacology of Fluid & Electrolyte Balance

- **Background**
- **Replacement fluids**
- **Other drugs**

BY: ABUBAKR M. EL-MAHMOUDY, PhD

Background:

- ☒ Body water consists of 60-70% of body weight.
- ☒ It contains three compartments:
  - o Extra cellular fluid and plasma (22.5%).
  - o Intracellular fluid (cytoplasm; 75%)
  - o Transcellular fluid (aqueous humor, CSF, synovial fluid,...etc.; 2.5%)

Drugs affecting water and electrolyte balance are classified according to their nature of action into:

a. Replacement fluids.
b. Mineralocorticoids.
c. Diuretics.
d. Anti-diuretics.
e. Anti-diuretic hormone.

a. Replacement fluids

Def.: These are the drugs which compensate lost body fluids and electrolytes.

The loss of body fluid can be treated by:

1. Arresting the fluid loss or haemorrhage.

2. Restoring the electrolyte balance by:

- ☒ Normal saline.
- ☒ Ringer's solution > in gastrointestinal disturbances.
- ☒ Ringer's lactate > in case of acidosis. It may be injected with glucose 10 % in case of debility.
- ☒ THAM (tris hydroxymethyl amino methane) > also in case of acidosis.

Defect repair

This means replacing the lost electrolyte when it is well specified as follows:

- Intestinal fluid replacement (Na^+, Cl^-, HCO_3^-)
- Gastric fluid replacement (mainly Cl^-)
- Talbot's solution: in case of inavailability of the previous two solutions; and no severe deficiency and it is good source for all electrolytes.

3. Restoring blood volume in case of blood loss (i.e. internal or external hemorrhage, burns, or plasma loss) the following fluids can be used:

A. Plasma expanders

1. Whole blood (matching should be checked)
2. Blood plasma (100 ml of 3% Na citrate)
   In burns, trauma and surgery
3. Blood serum (rare)

B. Plasma substituents

They should:-

- Have molecular weight similar to plasma (iso-osmotic)
- Persist in circulation for long time.
- Cleared at the same rate of albumin.

Examples are:

1. Gelatin 6% solution
2. Dextrans (glucopolysaccharide) with histamine release as a side effect (rebound hypotension), for example:

   Dextran 70: Its molecular weight is 70000

   Dextran 40: Its molecular weight is 40000 (histamine releaser)
3. Polyvinyl pyrrolidone (PVP):

   Its molecular weight 30000 (releases more histamine)

b. Mineralocorticoids.

c. Diuretics.

d. Anti-diuretics.

e. Anti-diuretic hormone

The previous 4 groups have been mentioned earlier; please refer to their corresponding sections.

XIV. Pharmacology of Growth promotion

- **Definition & remarks**
- **Hormonal growth promotants**
- **Antimicrobial growth promotants**
- **Probiotics**

BY: DR. HOWAIDA M. EL-KHOLY, PhD
LECTURER OF PHARMACOLOGY

Growth promotants
(Growth Enhancers)

Def.: are the drugs that increase the feed conversion rate in food producing animals meaning increase the ratio of high quality human food produced without causing any significant risk into the consumer, and with the use of the same amount of food given to the animal.

NB:

1. Recently, consumer concerns about the feed additives are focusing on the animal safety and the potential human hazards of using that food.
2. Promotion at the young age yields increase in the muscle, and bone size and the amount of fat while promotion after puberty yields increase in the fat ratio.
3. Flushing means giving more ration than it is used to be. It could be before the breeding season or before marketing of the animal.

<u>Growth promotion of animal could be achieved by using:</u>

I. Hormonal

II. Antimicrobial

III. Pobiotics

I. Hormonal

The trick of it is by increasing the nutrient partitioning to the muscle.

1. **Sex hormones**

The principle rules:

- Using which hormone depends on determination which animal sex, age and conditions.
- What will be used is the hormone that will replace the deficient one in the animal to be treated.
- Estrogen and testosterone are not intended for use in breeding males and females respectively.
- Testosterones are not used solely as anabolic as they have strong effect on the animal behavior and their anabolic response is not big. But progesterone and testosterone are given in combination with the estrogens in the compressed pellets implants to prolong their actions and neutralize their feminine action.

Endogenous Steroids:

The steroidal compounds used for anabolic purposes in food animals are estradiol, progesterone, and testosterone. **Testosterone binds to receptors in muscle and stimulates them** increasing incorporation of amino acids into protein, thereby increasing muscle mass without increasing in the adipose tissue and **estradiol acts by stimulation of the somatotropic axis** to increase growth hormone and thus insulin-like-growth factor (IGF-1) production and availability by modulation of the IGF binding proteins. Naturally produced endogenous steroids are not orally active and very low concentration in the blood can produce physiologic effects, and can transiently affect the behavior of treated animals. The major use of progesterone is to slow the release of estradiol from compressed pellet implants.

Synthetic Steroids: synthetic steroids are commercially available because of their efficacy, their relatively mild androgenicity, and because they cause few behavioral anomalies. Commercial synthetic steroids are androgenic, (trembelone acetate, TBA), or progestogenic (melengestrol acetate, MGA).

Synthetic nonsteroid: they include the estrogen like products, such as stilbene and zeranol.

Applications: sex hormones: are used as anabolics in cattle, sheep and pigs by increasing the nitrogen retention but in poultry they increase the fat deposition and stay for a longer time than the life span of the bird!

2. **Growth Hormone (GH):**

- The most commonly used peptide to enhance growth and production
- Its chemical structure is species-specific
- It has a short half-life (20-30 min).
- Not orally active and is rapidly digested and cleared by the gut, liver, and kidney; thus, it must be administered via a parenteral route.
- Sustained-release (14-28 days) formulations have been developed for use in cattle to overcome the need for daily injections.
- When administered to cattle, GH increases growth rate (5-10%), feed conversion efficiency, and the carcass lean to fat ratio.
- Gender has little effect on response
- Response to GH is lower in older animals with greater fat deposition.
- Using of growth hormone needs specific nutritional requirements as protein level and certain amino acids contents.
- It has excellent effect in cattle, sheep and pigs put not in poultry.

3. **β-Adrenergic agonists (β-AA):**

- The β_3 adrenergic receptors are present in the brown adipose tissue.
- Their activation leads to **lipolysis** of that brown adipose tissue and protection of the mass muscle tissue from degradation leading to **increase in muscle mass** and increase in protein synthesis.
- Examples: Phenethanolamines
- The major use is in cattle and sheep, the lean contents increase by 10-20% and the fat contents decrease by 7-20%
- The meat produced in that condition is **tough (lack of marbling)**
- They are active orally.
- Of low side effects.

II. Antimicrobial feed additives

- By inhibiting the sub-clinical infection of the animal or the change in the direction of the microbial fermentation of the rumen will increase the animal productivity and decrease the losses.
- In the livestock antimicrobials are used in male and female animals without adverse effects on ovarian and testicular development or function because they are poorly absorbed.
- Unlike anabolic steroids, they do not affect carcass composition.
- Antimicrobials are commonly used in conjunction with estradiol, zeranol, or TBA, and generally their combined effects are additive.

1. Ionophore antibiotics:

- Examples: monensin, lasalocid and salinomycin
- Mode of action: modify the movement of monovalent (sodium and potassium) and divalent (calcium) ions across biologic membranes, modify the rumen microflora, decrease acetate and methane production,

increase propionate, may improve nitrogen utilization, and can increase dry matter digestibility in ruminants.

- Their main effect is to increase feed efficiency so improve growth rates of ruminants on high-roughage diets.
- Some ionophores also have a therapeutic use (eg, monensin for prevention of coccidiosis in poultry).
- They are characterized by a very short withdrawal time (3 days at maximum)

2. Non-ionophore antibiotics:

- Examples: bacitracin, carbodox, olaqûindox, tylosin, virginiamycin, avilamycin and flavophospholipol.
- Some alter the ruminal microflora by inhibiting the G-ve bacteria and inhibit the polyglycan formation leading effect similar to the ionophores.
- Some produce there effect by combating the little infections leading to amino acids sparing for growth.
- Many of these antimicrobials are banned due to the microbial resistance originated from the sub-therapeutic level for these antibiotics.
- Some of them have a long withdrawal time and that will increase the risk of residue effects by consuming the products.
- Growth promotion using the antimicrobials decreases by optimizing the conditions and improving the animal housing and hygiene.

III. Probiotics

- There is a balance between the beneficial and pathogenic microorganisms.
- Under some conditions the pathogenic microorganisms overcome the beneficial ones.
- Yeast and lactic acid producing bacteria are good in preventing that subject.
- Examples: selected strains of lactobacilli and streptococci and yeast that alter the microbial species present in the GI system to the benefit of the treated animal.
- They help overcome the upset gut due to weaning or transport saving the food energy and amino acid for lean production rather than combating the microorganisms.
- The presence of active acid forming microflora inhibit the pathogenic bacteria from colonization in the gut.

XV. CHEMOTHERAPY

XV.I. ANTIBACTERIAL DRUGS

- **Principles**
- **Sulphonamides**
- **Antibiotics**
- **Synthetic antibacterials**

BY: PROF. DR. MOSSAD G. A. EL-SAYED, PhD
PROFESSOR OF PHARMACOLOGY

I. SELECTION OF ANTIMICROBIAL AGENTS

Selection of the most appropriate antimicrobial agent requires knowledge of 1) the organism's identity, 2) its susceptibility to a particular agent, 3) the site of the infection, 4) patient factors, 5) the safety of the agent, and 6) the cost of therapy.

A. Identification of the infecting organism

Characterization of the organism is central to selection of the proper drug. A rapid assessment of the nature of the pathogen can sometimes be made on the basis of the Gram stain, which is particularly useful in identifying the presence and morphologic features of microorganisms in body fluids that are normally sterile (cerebrospinal fluid, pleural fluid, synovial fluid, peritoneal fluid, and urine). It is generally necessary to culture the infective organism to arrive at a conclusive diagnosis and to determine the susceptibility of the bacteria to antimicrobial agents. Thus, it is essential to obtain a sample culture of the organism prior to initiating treatment.

B. Empiric therapy prior to identification of the organism

The antimicrobial agent used to treat an infection is selected after the organism has been identified and its drug susceptibility established. However, in the critically ill patient, such a delay could prove fatal, and immediate empiric therapy is indicated.

Broad-spectrum therapy may be needed initially for serious infections when the identity of the organism is unknown or the site makes a polymicrobial infection likely. The choice of agents may also be guided by known association of particular organisms with infection in a given clinical setting.

C. Determination of antimicrobial susceptibility of infective organisms

After a pathogen is cultured, its susceptibility to specific antibiotics serves as a guide in choosing antimicrobial therapy. The minimum inhibitory and bactericidal concentrations of a drug can be experimentally determined.

1. **Bacteriostatic vs. bactericidal drugs**: Antimicrobial drugs are classified as either bacteriostatic or bactericidal. Bacteriostatic drugs arrest the growth and replication of bacteria at serum levels achievable in the patient, thus limiting the spread of infection while the body's immune system attacks, immobilizes, and eliminates the pathogens. If the drug is removed before the immune system has scavenged the organisms, enough viable organisms may remain to begin a second cycle of infection. Bactericidal drugs kill bacteria at drug serum levels achievable in the patient. Because of their more aggressive antimicrobial action, these agents are often the drugs of choice in seriously ill patients. Figure (40) shows a laboratory experiment in which the growth of bacteria is arrested by the addition of a bacteriostatic agent. Note that viable organisms remain even in the presence of the bacteriostatic drug. By contrast,

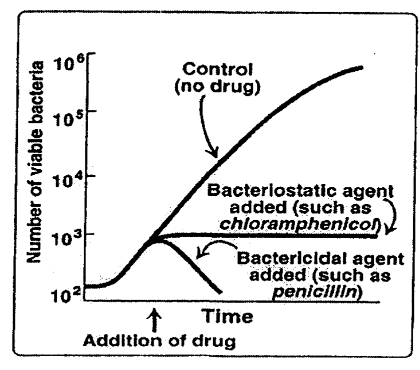


Figure (40): Effects of bactericidal and bacteriostatic drugs of the growth of bacteria *in vitro.*

addition of a bactericidal agent kills bacteria, and the total number of viable organisms decreases. Although practical, this classification may be too simplistic, because it is possible for an antibiotic to be bacteriostatic for one organism and bactericidal for another. For example, chloramphenicol is static against gram-negative rods and is cidal against other organisms, such as *S. pneumoniae*.

2. **Minimum inhibitory concentration**: To determine the minimum inhibitory concentration (MIC), tubes containing serial dilutions of an antibiotic are inoculated with the organism whose susceptibility is to be tested. The tubes are incubated and later observed to determine the MIC - that is, the lowest concentration of antibiotic that inhibits bacterial growth. To provide effective antimicrobial therapy, the clinically obtainable antibiotic concentration in body fluids should be greater than the MIC.

3. **Minimum bactericidal concentration**: This quantitative assay determines the minimal concentration of antibiotic that kills the bacteria under investigation. The tubes that show no growth in the MIC assay are subcultured into antibiotic-free media. The minimum bactericidal concentration (MBC) is the lowest concentration of antimicrobial agent that results in a 99.9 percent decline in colony count after overnight broth dilution incubations.

D. Effect of the site of infection on therapy: The blood-brain barrier

Adequate levels of an antibiotic must reach the site of infection for the invading microorganisms to be effectively eradicated. Capillaries with varying degrees of permeability carry drugs to the body tissues. For example, the endothelial cells comprising the walls of capillaries of many tissues have fenestrations (openings that act like windows) that allow most drugs not bound by plasma proteins to penetrate. However, natural barriers to drug delivery are created by the structures of the capillaries of some tissues, such as the prostate, the vitreous body of the eye, and the central nervous system. Of particular significance are the capillaries in the brain, which help to create and maintain the blood-brain barrier. This barrier is formed by the single layer of tile-like endothelial cells fused by tight junctions that impede entry from the blood to the brain of virtually all molecules, except those that are small and lipophilic.

The penetration and concentration of an antibacterial agent in the CSF is particularly influenced by the following:

1. **Lipid solubility of the drug:** All compounds without a specific transporter must pass intracellularly from the blood to the CSF (through two endothelial cell membranes). The lipid solubility of a drug is therefore a major determinant of its ability to penetrate into the brain. For example,

lipid-soluble drugs, such as the quinolones and metronidazole, have significant penetration into the CNS. In contrast, β-lactam antibiotics, such as penicillin, are ionized at physiologic pH and have low solubility in lipids. They therefore have limited penetration through the intact blood-brain barrier under normal circumstances. In infections such as meningitis, in which the brain becomes inflamed, the barrier does not function effectively, and local permeability is increased. Some β-lactam antibiotics can then enter the CSF in therapeutic amounts.

2. **Molecular weight of the drug:** A compound with a low molecular weight has an enhanced ability to cross the blood-brain barrier, whereas compounds with a high molecular weight (for example, vancomycin) penetrate poorly, even in the presence of meningeal inflammation.

3. **Protein binding of the drug:** A high degree of protein binding of a drug in the serum restricts its entry into the CSF. It therefore is the amount of free (unbound) drug in serum, rather than the total amount of drug present, that is important for CSF penetration.

E. Patient factors

In selecting an antibiotic, attention must be paid to the condition of the patient. For example, the status of the patient's immune system, kidneys, liver, circulation, and age must be considered. In pregnancy or breast-feeding young also affects selection of the antimicrobial agent.

1. **Immune system:** Elimination of infecting organisms from the body depends on an intact immune system. Antibacterial drugs decrease the microbial population (bactericidal) or inhibit further bacterial growth (bacteriostatic), but the host defense system must ultimately eliminate the invading organisms. Higher-than-usual doses of bactericidal agents or

longer courses of treatment are required to eliminate infective organisms in these individuals.

2. **Renal dysfunction:** Poor kidney function (ten percent or less of normal) causes accumulation in the body of antibiotics that ordinarily are eliminated by this route. This may lead to serious adverse effects unless drug accumulation is controlled by adjusting the dose or the dosage schedule of the antibiotic.

3. **Hepatic dysfunction**: Antibiotics that are concentrated or eliminated by the liver (for example, erythromycin and tetracycline) are contraindicated in treating patients with liver disease.

4. **Age**: Renal or hepatic elimination processes are often poorly developed in newborns, making neonates particularly vulnerable to the toxic effects of chloramphenicol and sultonamides. Young should not be treated with tetracyclines, which affect bone growth.

5. **Pregnancy**: All antibiotics cross the placenta. Adverse effects to the fetus are rare, except for tooth dysplasia and inhibition of bone growth encountered with the tetracyclines. However, some anthelmintics are embryotoxic and teratogenic. Aminoglycosides should be avoided in pregnancy because of their ototoxic effect on the fetus.

6. **Lactation**: Drugs administered to a lactating may enter the nursing the breast milk. Although the concentration of an antibiotic in breast milk is usually low, the total dose to the infant may be enough to cause problems.

F. Safety of the agent

Many of the antibiotics, such as the penicillins, are among the least toxic of all drugs, because they interfere with a site unique to the growth of microorganisms. Other antimicrobial agents (for example, chloramphenicol

are less microorganism-specific, and are reserved for life-threatening infections because of the drug's potential for serious toxicity to the patient.

G. Cost of therapy

Often, several drugs may show similar efficacy in treating an infection but vary widely in cost. None of these agents shows a clear therapeutic superiority; thus, a combination of metronidazole with bismuth subsalicylate plus one other antibiotic is usually employed in the treatment of *Helicobacter pylori*-induced peptic ulcers. Selecting clarithromycin instead as the drug of choice would clearly make a considerable cost impact.

II. ROUTE OF ADMINISTRATION

The oral route of administration is chosen for infections that are mild and can be treated on an outpatient basis. In addition, economic pressures have prompted the use of oral antibiotic therapy in all but the most serious infectious diseases. In patients requiring a course of intravenous therapy initially, the switch to oral agents occurs as soon as possible. However, some antibiotics, such as vancomycin, the aminoglycosides, and amphotercin are so poorly absorbed from the gastrointestinal tract that adequate serum revels cannot be obtained by oral administration. Parenteral administration is used for drugs that are poorly absorbed from the gastrointestinal tract, and for treatment of patients with serious infections, for whom it is necessary to maintain higher serum concentrations of antimicrobial agents than can be reliably obtained by the oral route.

III. DETERMINANTS OF RATIONAL DOSING

Rational dosing of antimicrobial agents is based on their pharmacodynamics (the relationship of drug concentrations to antimicrobial effects) as well as their pharmacokinetic properties (the absorption, distribution, and elimination of the drug by the body). Two important pharmacodynamic properties that have a significant influence on the frequency of dosing are concentration-dependent killing and post-antibiotic effect.

A. Concentration-dependent killing

Certain antimicrobial agents, including aminoglycosides and fluoroquinolones, show a significant increase in the rate of bacterial killing as the concentration of antiblotic- increases from 4- to 64-fold the MIC of the drug for the infecting organism. Giving drugs that exhibit this concentration-

dependent killing by a orice-a-day bolus infusion achieves high peak levels, favoring rapid killing of; the infecting pathogen. By contrast, p-lactams, glycopeptides, macrolides, and clindamycin do not exhibit this property; that is, increasing the concentration of antibiotic to higher multiples of the MIC does not significantly increase the rate of kill. The clinical efficacy of antimicrobials that have a nonsignificant, dose-dependent killing effect is best predicted by the percentage of time that blood concentrations of a drug remain above the MIC. This effect is sometimes called concentration-independent or time-dependent killing. For example, for the penicillins and cephalosporins, dosing schedules that, ensure blood levels greater than the MIC sixty to seventy percent of the time have been demonstrated to be clinically effective, Some experts therefore suggest that some severe infections are best treated by continuous infusion of these agents rather than by intermittent dosing.

B. Post-antibiotic effect

The post-antibiotic effect (PAE) is a persistent suppression of microbial growth that occurs after levels of antibiotic have fallen below the MIC. To measure the PAE of an antibiotic, a test culture is first incubated in antibiotic-containing medium and then transferred to antibiotic-free medium. The PAE is defined as the length of time it takes (after the transfer) for the culture to achieve log phase growth. Antimicrobial drugs exhibiting a long PAE (several hours) often require only one dose per day. For example, antimicrobials such as aminoglycosides and fluoroquinolones exhibit a long PAE, particularly against gram-negative bacteria.

IV. CHEMOTHERAPEUTIC SPECTRA

A. Narrow-spectrum antibiotics

Chemotherapeutic agents acting only on a single or a limited group of microorganisms are said to have a narrow spectrum.

B. Extended-spectrum antibiotics

Extended spectrum is the term applied to antibiotics that are effective against gram-positive organisms and also against a significant number of gram-negative bacteria. For example, ampicillin is considered to have an extended spectrum, because it acts against gram-positive and some gram-negative bacteria.

C. Broad-spectrum antibiotics

Drugs such as tetracyctine and chloramphenicol affect a wide variety of microbial species and are referred to as broad-spectrum antibiotics. Administration of broad-spectrum antibiotics can drastically alter the nature of the normal bacterial flora, and precipitate a superinfection of an organism such as *Candida albicans*, the growth of which is normally kept in check by the presence of other microorganisms.

V. COMBINATIONS OF ANTIMICROBIAL DRUGS

It is therapeutically advisable to treat patients with the single agent that is most specific for the infecting organism. This strategy reduces the possibility of superinfection, decreases the emergence of resistant organisms and minimizes toxicity. However, situations in which combinations of drugs are employed do exist.

A. Advantages of drug combinations

Certain combinations of antibiotics, such as β-lactams and aminoglycosides, show synergism; that is, the combination is more effective than either of the drugs used separately. Because such synergism among antimicrobial agents is rare, multiple drugs used in combination are only indicated in special situations — for example, when an infection is of unknown origin.

B. Disadvantages of drug combinations

A number of antibiotics act only when organisms are multiplying. Thus, coadministration of an agent that causes bacteriostasis plus a second agent that is bactericidal may result in the first drug interfering with the action of the second.

VI. DRUG RESISTANCE

Bacteria are said to be resistant to an antibiotic if their growth is not halted by the maximal level of that antibiotic that can be tolerated by the host. Some organisms are inherently resistant to an antibiotic. For example, gram-negative organisms are inherently resistant to vancomycin. However, microbial species that are normally responsive to a particular drug may develop more virulent, resistant strains through spontaneous mutation or acquired resistance and selection. Some of these strains, may even become resistant to more than one antibiotic.

A. Genetic alterations leading to drug resistance

Acquired antibiotic resistance requires the temporary or permanent gain or alteration of bacterial genetic information. Resistance develops due to the ability of DNA to undergo spontaneous mutation or to move from one organism to another (Figure 41).

1. **Spontaneous mutations of DNA:** Chromosomal alteration may occur by insertion, deletion, or substitution of one or more nucleotides within the genome. The resulting mutation may persist, be corrected by the organism, or be lethal to the cell. If the cell survives, it can replicate and transmit its mutated properties to progeny cells. Some spontaneous mutations have little or no effect on the susceptibility of the organism to antimicrobial agents. However, mutations that produce antibiotic-resistant strains can result in organisms that may proliferate under certain selective pressures. An example is the emergence of rifampin-resistant *Mycobacterium tuberculosis* when rifampin is used as a single antibiotic.
2. **DNA transfer of drug resistance:** Of particular clinical concern is resistance acquired due to DNA transfer from one bacterium to another. Resistance properties are usually encoded in extra-chromosomal R factors **(resistance plasmids).** In fact, most resistance genes are plasmid mediated, although plasmid-mediated traits can become incorporated into host bacterial DNA. Plasmids may enter cells by processes such as transduction (phage mediated), transformation, or bacterial conjugation.

B. Altered expression of proteins in drug-resistant organisms

Drug resistance may be mediated by a variety of mechanisms, such as a lack of or an alteration in an antibiotic target site, lowered penetrability of the drug due to decreased permeability, increased efflux of the drug, or presence of antibiotic-inactivating enzymes.

1. **Modification of target sites**: Alteration of an antibiotic's target site through mutation can confer organismal resistance to one or more related antibiotics. For example, *S. pneumoniae* resistance to β-lactam antibiotics involves alterations in one or more of the major; bacterial penicillin-

binding proteins, resulting in decreased binding of the antibiotic to its target.

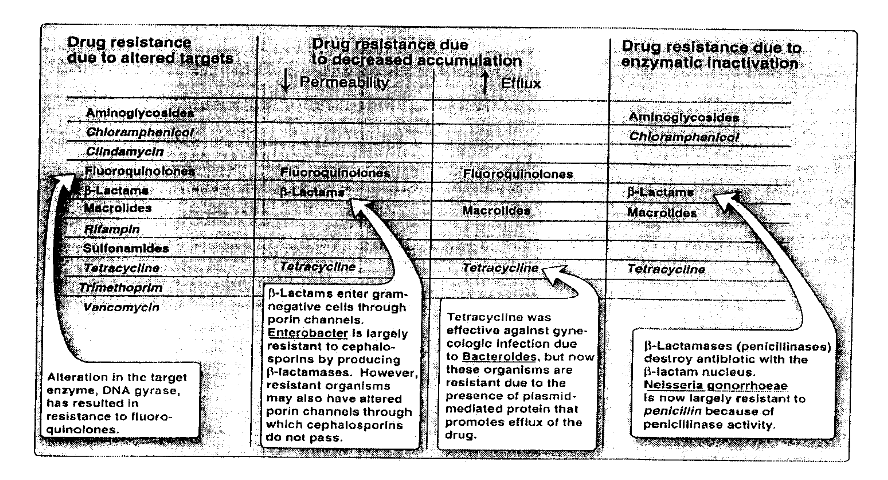


Figure (41): Some mechanisms of resistance to antibiotics.

2. **Decreased accumulation:** Decreased uptake or increased efflux of an antibiotic can confer resistance, because the drug is unable to attain access to the site of its action in sufficient concentrations, to injure or kill the organism. For example, gram-negative organisms can limit the penetration of certain agents, including β-lactam antibiotics, tetracyclines, and chloramphenicol, as a result of an alteration in the number and structure of porins (channels) in the outer membrane. Also, the presence of an efflux pump can limit levels of a drug in an organism.

3. **Enzymic inactivation:** The ability to destroy or inactivate the antimicrobial agent can also confer resistance on microorganisms. Examples of antibiotic-inactivating enzymes include 1) (3-lactamases

("penicillinases") that hydrolytically inactivate the-β-lactam ring of penicillins', cephalosporins, and related drugs; 2) acetyltransferases that transfer an acetyl group to the antibiotic, inactivating choramphenicol or aminoglycosides; and 3) esterases that hydrolyze the lactone ring of macrolides.

VII. COMPLICATIONS OF ANTIBIOTIC THERAPY

Because the mechanism of action of a particular antibiotic is selectively toxic to an invading organism does not insure the host against adverse effects. For example, the drug may produce an allergic response or be toxic in ways unrelated to the drug's antimicrobial activity.

A. Hypersensitivity

Hypersensitivity reactions to antimicrobial drugs or their metabolic products frequently occur. For example, the penicillins, despite their almost absolute selective microbial toxicity, can cause serious hypersensitivity problems, ranging from urticaria to anaphylactic shock.

B. Direct toxicity

High serum levels of certain antibiotics may cause toxicity by directly affecting cellular processes in the host. For example, amino-giycosides can cause ototoxtcity by interfering with membrane function in the hair cells of the organ of Corti.

C. Superinfections

Drug therapy, particularly with broad-spectrum antimicrobials or combinations of agents, can lead to alterations of the normal microbial flora of the upper respiratory, intestinal, and genitourinary tracts, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria. These infections are often difficult to treat.

VIII. Classification OF ANTIMICROBIAL AGENTS

Antimicrobial drugs can be classified in a number of ways. These include 1) by their chemical structure (for example, β-lactams or amino-glycosides)

Classification of antibiotics according to chemical structure:

1- Penicilins and cephalosporins:

- Short acting e.g. benzylpenicillin.
- Long acting e.g. procaine penicillin, benthamine penicillin.
- Semi – synthetic.
  - Orally active e.g. phenoxymethylpenicillin.
  - Penicillinase resistant penicillin e.g. methicillin, cloxacillin.
  - Broad spectrum penicillins e.g. ampicillin, carbenicillin.

2- Aminoglycoside antibiotics:

Streptomycin, neomycin, kanamycin, gentamycin, framycetin.

3- Macrolide antibiotics:

Erythromycin, oleandomycin, spiramycin, tylosin.

4- Tetracyclines:

5- Antibiotics of miscellaneous structures:

Chloramphenicol, lincomycin, novobiocin, polymyxin B & E (colistin), Bacetracin.

2) by their mechanism of action (for example, cell wall synthesis inhibitors) (Figure 42) or 3) by their activity against particular types of organisms (for example, bacteria, fungi, or viruses).

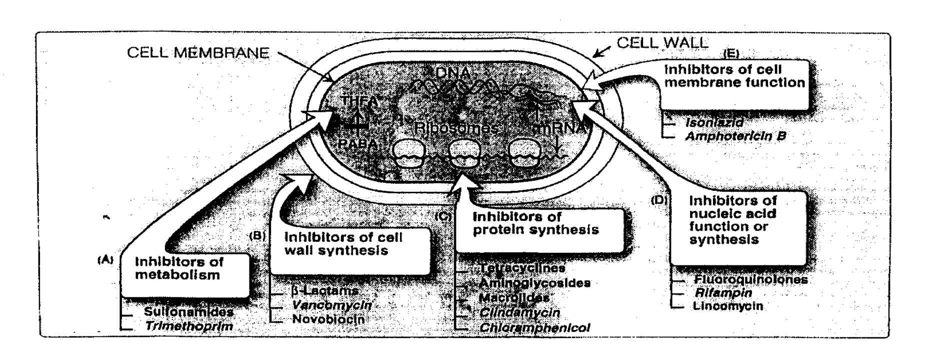


Figure (42): Classification of some antibacterial agents by their sites of action. (THFA = Tetrahydrofolic acid; PABA = para amino benzoic acid)

A- INHIBITORS OF METABOLISM

1. Sulphonamides

The sulphonamides are a group of complex synthetic organic chemical compounds with chemotherapeutic activity. They have a common chemical nucleus which is essential for antibacterial activity. This nucleus is very closely related to para-amino benzoic acid, an essential member of the vitamin B complex.



Sulphanilamide **P-amino-benzoic acid**

The group can be divided into two main sections according to the site of therapeutic action.

1. The **systemic** sulphonamides, which are absorbed reasonably well from the intestines. The most important of these are sulphanilamide, sulphacetamide, sulphapyridine, sulphadimidine, sulphathiazole, sulphamerazine sulphadiazine, sulphaquinoxaline (used only in poultry).
2. The so-called **"gut-active"** sulphonamides, which are poorly absorbed from the intestines and exert their effect locally in the gut. Examples are sulphaguanidine, phthalylsulphathiazole, succinylsulphathiazole and phthalylsulphacetamide.

Chemical and physical properties

1. All sulphonamides are white crystalline compound but sulphaquinoxaline in yellow.
2. They have a weak acidic properties and forming salt with strong base.

3. They are sparingly or insoluble in water but the sodium salt is soluble in water and employed for i.v. injection. The sodium salts are not recommended to be given orally for their high alkalinity but some preparation of pH approach neutrality can be given.

Absorption:

Most of sulphonamides are absorbed from the intestinal tract except the gut-active sulphonamides. The extent and rate of absorption depend upon:

1. **Type of sulphonamide:** the absorbability is not related to its solubility in water e.g. phthalylsulpathiazole is relatively soluble but poorly absorbed, whereas aulphadiazine is poorly soluble in water and yet is absorbed well.

2. **Species of animals:**

The sulphonamides are absorbed from the digestive tract more rapidly and completely in carnivora than in herbivora.

The monosodium salts are given by all routes of injection except the intravenous one and maximum blood level rapidly achieved. These salts can be given in drinking water but should be suitably buffered to prevent decomposition. The disodium salts may be given via all routes of injection.

Blood levels:

Blood and tissues to level of sulphonamides are of great importance to exert the antibacterial effect. Blood levels of 8-15 mg/100 ml blood in man and 5 mg/100 ml in animals are taken as being therapeutically effective. Once adequate blood levels have been established, oral dosing every 8 hours in simple stomached animals and 12 hours in adult ruminants is sufficient to maintain them, although with long acting sulphonamides (as sulphamethyl-phenazole) daily dosing is sufficient to maintain adequate blood levels. Large

dose are usually given to establish therapeutic blood and tissue level initially, but subsequent doses are similar.

Barriers:

Sulphonamides can diffuse very widely into the tissue penetrating into all body fluids.

1. **Blood brain barriers:** is governed by the proportion of sulphonamide which is circulating in the blood combined with protein or in an acetylated form. Although sulpadimidine diffuse into the cerebrospinal fluid sulphadiazine and sulphamerzine are superior and they are preferred for the treatment of meningeal and brain infections. Sulphathiazol penetrates poorly, when compared with other sulphonamides.
2. **Other barrier:**

With exception of the blood-brain barrier, all other natural barriers are passed and effective concentrations appear in all tissues, body cavities and secretions including urine, bile and milk. Sulphonamide passes also to placenta.

Metabolism:

Sulphonamides undergo metabolic alteration in the tissue especially in the liver, where acetylation and oxidation occur. Acetylation is carried out by the aids of the acetylase enzymes. The acetylated from have no antibacterial activity, less soluble and lead to crystalluria and renal calculi formation. The oxidative products are responsible for many of the toxic reaction as skin rash and hypersensitivity.

Excretion:

The sulphonamides are excreted mainly via the kidney. They are excreted either in an unchanged form or as conjugated excretory metabolites, which has reduced antibacterial activity. Some sulpha drugs are excreted in the milk and bile.

Actions and mode of action:

Sulphonamides in low therapeutic concentration are bacteriostatics and in high therapeutic concentrations are bacteriocidal. The mode of action is an example of competitive inhibition. Para-aminobenzoic acid (PABA) is an essential for the synthesis of folic acid. The latter is important for the synthesis of purines in the bacteria. Due to the chemical similarity between sulphonamides and PABA, sulphonamides can enter into the reaction in place of PABA and compete for the active center of the enzyme. As a result nonfunctional analogues of folio acid are formed, preventing further growth of the bacterial cell (Figure 43).

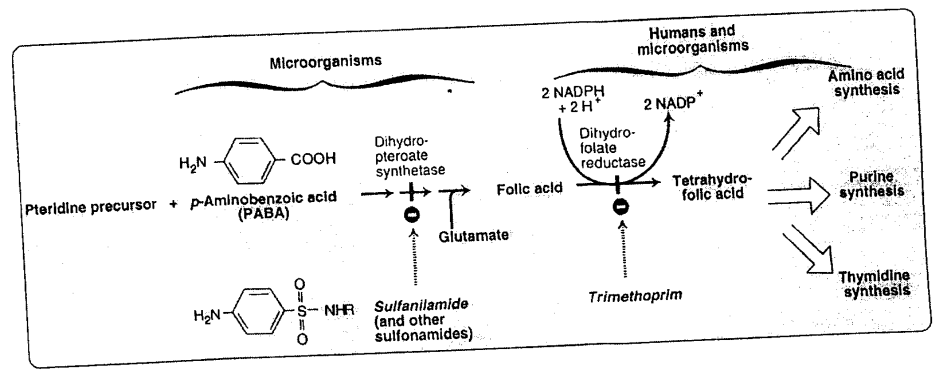


Figure (43): Inhibition of tetrahydrofolate reductase synthesis by sulphonamides and trimethoprim.

Antagonists:

The following interfere with the antibacterial activity of sulphonamides and considered an antagonist for sulpha drugs:

1. Para-aminobenzoic acid and related compounds as local anesthetics.
2. Members of vitamin B complex as nicotinamide, folic acid, and precursors of these including various amino acids e.g. glutamic acid and methionine.
3. Protein, which combine loosely with sulpha drug e.g. gelatin, albumin, peptone, and serum protein.
4. Coenzymes, glucose and mercuric chloride are all reported to possess to possess antagonistic action to sulpha drugs.

Bacterial resistance (Drug fastness):

Some bacteria are able, to synthesize folic acid but depend upon exogenous sources and for this reason are not succeptible to sulphonamide action (natural resistance). Some bacteria become unsusceptible to the effect of certain sulphonamide (acquired resistance). Sulphonamide resistant mutants occur in most susceptible bacterial populations. The mechanism of bacterial resistance to sulphonamides may be due to:

1. An increased capacity to destroy or inactivate the drug.
2. An alterative metabolic pathway for synthesis or degradation of an essential metabolite.
3. An increased production of an essential metabolite or drug antagonists.

Therapeutic uses of sulphonamides:

The clinical applications of sulphonamides are classified according to route of administration into:

1. **Topical**: to the wound, skin and mucous membrane is undesirable because of their low activity and high risk of allergic sensitization, but sulphacetmide solution (30%) or ointment (10%) are used for the treatment of conjunctivitis.

2. **Oral**: The insoluble nonabsorbable sulphonamides e.g. sulphaguanidine, succinylsulphathiazole (sulphasuxidine), and sulphathalidine are used for the treatment of calf scour, coccidiosis and ulceratlve colitis.

3. **Systemic:**

There are two types for systemic administration:

a) Rapidly absorbed and rapidly excreted sulphonamides:

These are used for urinary tract and acute systemic infection. After oral administration, 70 – 90% of the dose is rapidly absorbed within 3-4 hours. The free and acetylated forms of the drug are rapidly excreted and can be detected in the urine within 6 hours. By parenteral routes, they are quickly absorbed and excreted. Among this group are:

1. Sulphadiazine:

It is less toxic than other sulphonamide. It is given in a dose of 60 mg/kg b.wt. In poultry, it is mixed with the food in a concentration of 0.5%.

2. Sulphamerazine and sulphadimidine:

They are used for treatment of pneumonia, diphtheria, scour in calf, strangles in horses, mastitis, metritis in cattle and coccidiosis in poultry .

Dose: 100 mg/kg b.wt. (all animals), 0.4-0.5% in the food and 0.1-0.2 % sodium salt in water.

3. Sulphafurazole:

It is less toxic used for the treatment of urinary tract infection.

4. Sulphasomidine:

It is used for the treatment of tonsilitis, laryngitis, pharyngitis and sinusitis.

b. Rapidly absorbed and slowly excreted sulphonamides:

They remain for a long period until the drug is completely excreted. They are used as prophylactic and in chronic infection as gonorrhea, urinary infection with gram negative bacteria, bacillary dysentry and staphylococcus infection. Examples are sulphamethoxy-pyridazine, sulphamethoxazol, sulphadimethoxine and sulphaphenazol.

Dosage of sulphonamides:

The level of sulphonamides in the blood must be at least 5 mg/100 ml blood and 10 -12 mg/ 100 ml in sever infections.

Sulphonamides are given as initial dose 0.1 -0.2 g/kg/12 hour in the first day followed by maintenance dose (half the initial) for 5 days.

As bacteriostatic, sulphonamides should be administered for two days after the disappearance of the clinical symptoms, otherwise bacteria multiply again and relapse may result.

Toxicity :

Acute and chronic toxicity of sulpha drugs can be demonstrated either in man or in animals.

a. Acute toxicity: It is resulted from the massive administration of large doses of sulphonamides and it is characterized by nausea, temporary blindness, skin rashes, photosensitization, haemolytic anaemia and granulocytosis.

b. Chronic toxicity:

It assumes two forms; one is associated with depression of the intestinal flora and interferes with vitamin B metabolism, the other associated with crystaluria. The latter is less occurring in animals.

Continued administration of sulpha drugs in ruminants results in diarrhea, dehydration and debility with loss of appetite and milk yield. In other species, depression, nausea and vomition in animals that vomit.

How to minimize the toxicity of salphonamides:

It is done by:

1. Ingestion of large amount of water to ensure the volume of the urine that will keep the drug in solution. Sodium bicarbonate and citrate must be given because in the both free and acetylated forms are more soluble to avoid their precipitation.
2. Avoid U.V. and strong sun-light during treatment, because it may cause dermatitis.
3. X-rays should not be given to patient taken sulphonamides as it prevents the antibacterial effect of sulpha drugs.
4. Sulphates as magnesium and sodium sulphate are not given during the administration of sulpha drugs because they may cause sever reaction due to the formation of sulphameta-haemoglobin.
5. Sulpha drugs are contra-indicated in the presence of sulphur-containing foods.

Potentiated sulphonamides

It was demonstrated that trimethoprim and sulphonamides potentiated each other, with the result that together their antibacterial effects were greatly enhanced, and the therapeutic index was increased. The action of the combination proved to be bactericidal whereas the components separately were only bacteriostatic in action.

a. Two combinations are in use in various concentrations in the veterinary field: trimethoprirn + sulphadiazine and trimethoprim + sulfadoxine.

Mode of action:

Trimethoprim inhibits the bacterial dihydrofolate reductase (Figure 43).

Dosages:

1. Trivetrin injection: (40 mg trimethoprim + 200 mg sulphadoxine per 1 ml). It is injected in a dose of 1 ml/15 kg b.wt. daily.
2. Tribrissen injection (80 mg trimethoprim + 400 mg sulpha-diazine per 1 ml). It is injected in a dose of 1 ml /15 kg b.wt, daily. Tribrissen is present also in the form of bolus, powder, suspension and tablets.

b. Mixture of sulphadiazine, sulphathiazole and sulphamerazine produce a definite effect in reducing renal damage than when each member used alone.

c. Combined therapy of sulphonamide and antibiotics produces broad spectrum effect in the serum and gives better therapy.

B. INHIBITORS OF CELL WALL SYNTHESIS

I. OVERVIEW

Some antimicrobial drugs selectively interfere with synthesis of the bacterial cell wall—a structure that mammalian cells do not possess. The cell wall is a polymer called peptidoglycan that consists of glycan units joined to each other by peptide cross-links. To be maximally effective, inhibitors of cell wall synthesis require actively proliferating microorganisms; they have little or no effect on bacteria that are not growing and dividing. The most important members of this group of drugs are the (β-lactam antibiotics (named after the β-lactam ring that is essential to their activity) and vancomycin. Figure (44) shows the classification of agents affecting cell wall synthesis.

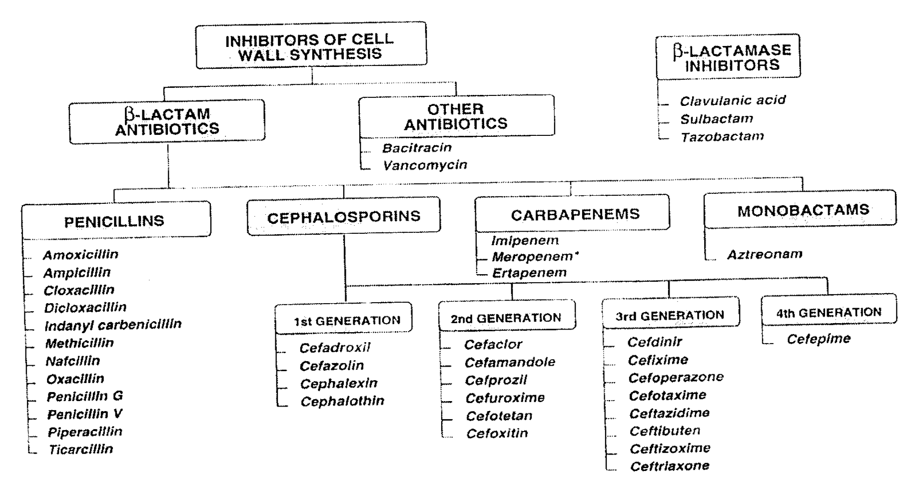


Figure (44): Summary of antimicrobial agents affecting cell wall synthesis.

II. PENICILLINS

Members of this family differ from one another in the R substituent attached to the 6-aminopenicillanic acid residue (Figure 45). The nature of this side chain affects the antimicrobial spectrum, stability to stomach acid, and susceptibility to bacterial degradative enzymes (β-lactamases).

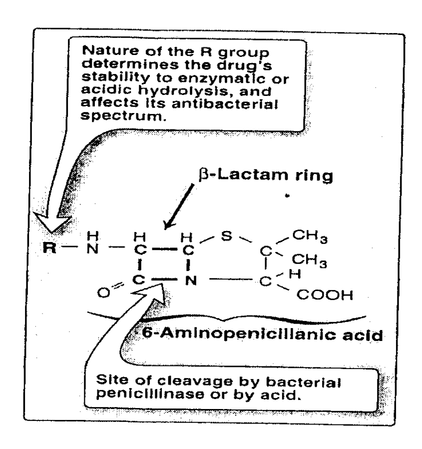


Figure (45): Structure features of β-lactam antibiotics

A. Mechanism of action

The penicillins interfere with the last step of bacterial cell wall synthesis (transpeptidation or cross-linkage), resulting in exposure of the osmotically less stable membrane. Cell lysis can then occur, either through osmotic pressure or through the activation of autolysins. These drugs are thus bactericidal. Penicillins are only effective against rapidly growing organisms that synthesize a peptidoglycan cell wall. Consequently, they are inactive against organisms devoid of this structure, such as mycobacteria, protozoa, fungi, and viruses.

1. **Penicillin-binding proteins:** Penicillins inactivate numerous proteins on the bacterial cell membrane. These penicillin-binding proteins (PBPs) are bacterial enzymes involved in the synthesis of the cell wall and in the maintenance of the morphologic features of the bacterium. Exposure to these antibiotics can therefore not only prevent cell wall synthesis, but also lead to morphologic changes or lysis of susceptible bacteria.

2. **Inhibition of transpeptidase:** Some PBPs catalyze formation of the cross-linkages between peptidoglycan chains. Penicillins inhibit this transpeptidase-catalyzed reaction, thus hindering the formation of cross-links essential for cell wall integrity.

3. **Production of autolysins:** The most recent mode of action involves release from the bacterial cell of lipotechoic acid, which appears to have the property of inhibiting an enzyme (murein hydrolase or autolysin) which is able to breakdown the cell wall. The lipotechoic acid prevents the action of autolysin. Penicillin helps the release of lipotechic acid and as a sequel, autolysin produces lysis of bacterial cell wall.

B. Antibacterial spectrum

In general, gram-positive microorganisms have cell walls that are easily traversed by penicillins and, therefore, in the absence of resistance are susceptible to these drugs. Gram-negative microorganisms have an outer lipopolysaccharide membrane surrounding the cell wall that presents a barrier to the water-soluble penicillins. However, gram-negative bacteria have proteins inserted in the lipopolysaccharide layer that act as water-filled channels (called porins) that permit transmembrane entry.

1. **Natural penicillins:** These penicillins, which include those listed as antistaphylococcal, are obtained from fermentations of the mold *Penicillium chrysogenum*. Other penicillins, such as ampicillin, are called

semisynthetic, because the different R groups are attached chemically to the 6-aminopenicillanic acid nucleus obtained from fermentation broths of the mold. Penicillin G (benzylpenicillin) is the cornerstone of therapy for infections caused by a number of Gram-positive and Gram-negative cocci, Gram-positive bacilli, and spirochetes (Figure 45). Penicillin G is susceptible to inactivation by β-lactamases (penicillinases). Penicillin V has a spectrum similar to that of penicillin G, but it is not used for treatment of bacteremia because of its higher minimum bactericidal concentration (the minimum amount of the drug needed to eliminate the infection. Penicillin V is more acid-stable than penicillin G. It is often employed in the treatment of oral infections, where it is effective against some anaerobic organisms.

2. **Antistaphylpcoccal penicillins:** Methicillin, nafcillin, oxacillin and dicloxacillin are penicillinase-resistant penicillins. Their use is restricted to the treatment of infections caused by penicillinase-producing staphylococci.

3. **Extended-spectrum penicillins:** Ampicillin and amoxicillin have an antibacterial spectrum similar to that of penicillin G, but are more effective against Gram-negative bacilli. They are therefore referred to as extended-spectrum penicillins.

4. **Antipseudomonal penicillins:** Indanyl carbenicillin, ticarcillin, and piperacillin are called antipseudomonal penicillins because of their activity against *Pseudomonas aeruginosa*. Piperacillin is the most potent of these antibiotics. They are effective against many Gram-negative bacilli, but not against *Klebsiella*, because of its constitutive penicillinase.

5. **Penicillins and aminoglycosides:** The antibacterial effects of all the β-lactam antibiotics are synergistic with the aminoglycosides. Because cell

wall synthesis inhibitors alter the permeability of bacterial cells, these drugs can facilitate the entry of other antibiotics (such as aminoglycosides) that might not ordinarily gain access to intracellular target sites. This can result in enhanced antimicrobial activity.

C. Resistance

Natural resistance to the penicillins occurs in organisms that either; lack a peptidoglycan cell wall (for example, the mycoplasma) or have cell walls that are impermeable to the drugs. Acquired resistance to the penicillins by plasmid transfer has become a significant clinical problem, because an organism may become resistant to several antibiotics at the same time due to distribution of a plasmid that encodes resistance to multiple agents. Multiplication of such an organism will lead to increased dissemination of the resistance genes. By obtaining a resistance plasmid, bacteria may acquire one or more of the following properties, thus allowing it to withstand β-lactam antibiotics.

1. **β-Lactamase activity:** This family of enzymes hydrolyzes the cyclic amide bond of the β-lactam ring, which results in loss of bactericidal activity (see Figure 46). They are the major cause of resistance to the penicillins, and are an increasing problem, β-Lactamases are either constitutive or, more commonly, are acquired by the transfer of plasmids. Some of the β-lactam antibiotics are poor substrates for β -lactamases and resist cleavage, thus retaining their activity against β-lactamase-producing organisms. Gram-positive organisms secrete β-lactamases extracellularly, whereas Gram-negative bacteria have the enzymes in the periplasmic space between the inner and outer membranes.

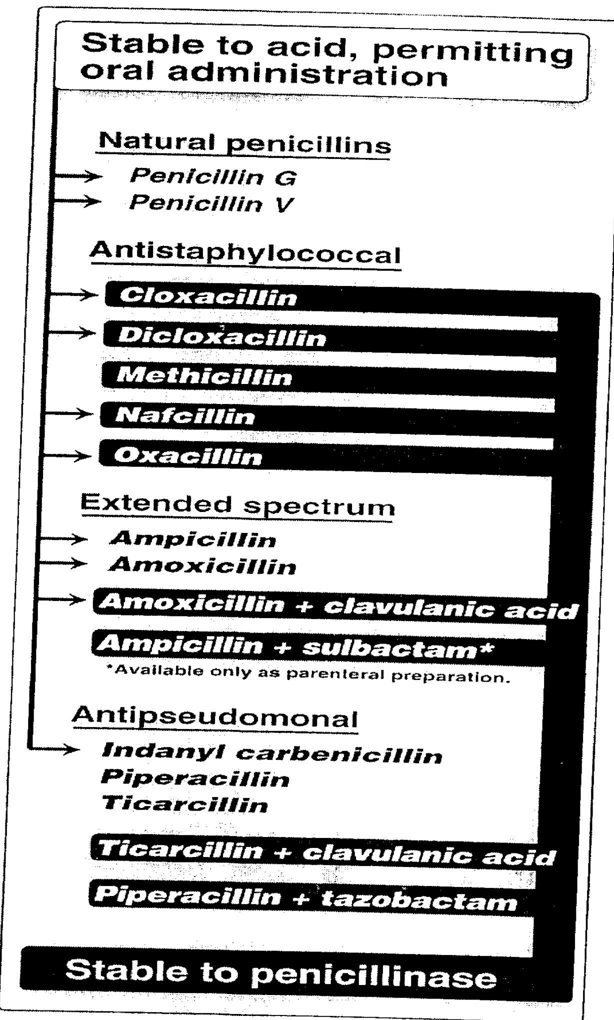


Figure (46): Resistance of penicillins to acid or action of penicillinase.

2. **Decreased permeability to the drug:** Decreased penetration of the antibiotic through the outer cell membrane prevents the drug from reaching the target PBPs. The presence of an efflux pump can also reduce the amount of intracellular drug.

3. **Altered PBPs**: Modified PBPs have a lower affinity for β-lactam antibiotics, requiring clinically unattainable concentrations of the drug to effect inhibition of bacterial growth.

D. Pharmacokinetics

Administration and absorption:

The sodium salt of penicillin is absorbed very rapidly from parentral injection sites when aquous solutions are used. Adequate blood levels are achieved within 30 min. from intramuscular sites. Delayed absorption is frequently required to maintain adequate antibiotic concentration in the blood and tissues. There are two methods of delaying absorption:

1- If inorganic salts are suspended in oil vehicles, they will diffuse out slowly e.g. sodium or calcium benzylpenicillin suspended in arachus oil with beeswax.

2- If sparingly soluble organic salts such procaine benzylpenicillin or benzathine penicillin are given as aquous suspensions with buffering and suspending agents, absorption is also slow and blood levels may be maintained for 24 to 48 h. with one injection.

If these two principles are combined so that insoluble penicillins are suspended in oil with aluminium monostearate, blood levels may be maintained for several days with one injection.

Phenoxymethyl penicillin (penicillin V) can be given orally, most probably as a means of maintaining blood levels after establishing them by parenteral injection.

Blood levels

The blood level required for all uses is 0.03 to 0.05 units per ml blood. These levels are bacteriostatic. 0.5 units per ml. is bactericidal. These levels in themselves are not important except that they are an indication of the levels in the tissues where the bacteria are multiplying, unless, of course, septicaemia is present.

Distribution:

Penicillin does not diffuse through the cerebrospinal fluid unless the meninges are inflammed. It does not readily pass from the maternal side to the faetal side unless the doses are large. It is slowly and irrigularly absorbed from the intestine. Penicillin diffuses poorly across serous membranes. Diffusion of penicillin into the milk in therapeutic concentration is achieved only by massive i.v. doses refractory mutants selected by exposure to the drug *in vitro* do not produce this enzyme, and the exact mechanism of their resistance is not known.

Toxicity:

There is no toxicity problem with penicillin in veterinary medicine. Occasionally allergic skin reactions may occur in small 5 animals and in thin skinned horses. Veterinary surgeons who are themselves sensitive to penicillin must use it with care. Where accidents have happened and penicillin sensitive human are affected. Antihistaminic are applied locally will counteract skin reactions but severe reactions should be referred to a

hospital. Animals showing allergy should be treated with antihistaminics locally and systematically.

Clinical applications

1. Bovine mastitis:

Penicillin G is used for the treatment of mastitis due to *Streptococcus agalactia.* To treat mastitis, it is used usual to administer penicillin in oil suspension intramammary via the teat sphinector, 300 000 units are introduced in each affected quarter which is milked out. It is usual to give three injections at intervals of 24 to 48 hr.

2. **Anthrax**: The general principle of therapy with penicillin is that a large initial dose must be given.

3. **Strangles:** A dosage of up to 100 000 units penicillin per kg body weight should be given daily for 5 days. *Streptococcus equi* responds to penicillin when the treatment is given at an early stage.

4. **Clostridial infections:** In tetenus, black leg and botulism, penicillin must be administered early in the course of the disease and where possible injected near the site of bacterial infection.

5. **Pyelonephritis**: due to *Corynebacterium renale.*

6. Non specific bacterial infection as naval infection in calves and foals which is often caused by streptococci. When the cause is *E. coli,* it is advisable to use a combination of penicillin and streptomycin.

7. Penicillin has been combined with sulphonamide for wound, burn and scald dressing.

Preparations of penicillins:

1. **Short acting penicillin:** Benzylpenicillin (Penicillin G): It is a widely used penicillin in veterinary practice produced from *P. Chrysogenum* in presence of phenyl acetic acid. It forms calcium and sodium salts which are very soluble. It is rapidly absorbed and excreted and penetrates the CSF.

Disadvantages of benzylpenicillin;

1) Unstable in acids, cannot be given orally.

2) Resistance of penicillinase producing organisms.

3) Narrow range of activity (G +ve and only some G –ve)

2. Long acting penicillins:

Procaine penicillin G.: It is a suspension of procaine penicillin in water. It is slowly absorbed and slowly excreted.

Benethamine penicillins: This is a long acting preparation given i.m. an insoluble suspension slowly releasing benzylpenicillin.

3. Semi-synthetic penicillins;

a) Orally active penicillins

Phenoxymethyl penicillin (penicillin V): It is produced from *P. chrysogenum* in presence of phenoxyacetic acid. It is stable in acid medium. It is suitable for oral administration in dogs and cats.

b) Penicillinase resistant penicillins:

Methicillin: It is a derivative of 6 aminopenicillanic acid and resistant to penicillinase, given by injection. It is less potent than benzylpenicillin and stimulates the production of penicillinase increasing resistant strains.

Gloxacillin: It is resistant to penicillinase and stable in acid medium.

c) **Broad spectrum penicillins:**

Ampicillin: It is the most important new penicillin. It is active against Gm +ve and Gm -ve. It is specially useful against coliforms resistant to tetracyclines and proteus, pseudomonas, salmonella, shigella and pasteurella which are not treated by any antibiotic. It is less potent than benzylpenicillin and not resistant to penicillinase. It is acid stable.

Carbenicillin; As ampicillin. It is unstable in acid, so given by injection.

Dosage :

Parenteral; 4000 to 10000 unit/kg body weight. The dose should be given every 4 hours, if a soluble salt in water is used, every 12 hr. if a soluble salt in oil and every 24 hr. if procaine penicillin is used in an oil suspension.

Oral; 3 to 4 times the parenteral dose or 100 000 to 300 000 units every 4 hr., if mineral or procaine salts are used. Phenoxymethyl penicillin is given at the rate of 8 mg/kg b.wt. three times daily. For pigs and poultry 16 mg.kg b.wt. twice daily is more convenient.

III . CEPHALOSPORINS

Def:- The cephalosporins are antibiotics related to penicillins, that are used in human and veterinary medicine to treat various infections caused by bacteria.

Cephalosporins have been used for a wide range of infections in various species.

They are not effective in the treatment of fungal infections or illnesses by viruses.

Generations of cephalosporin:-

There are four generations, the major differences in generations are:

1- increasing activity vs. various gram negative bacteria .

2- deceasing susceptibility to beta-lactamases.

First-generation have the highest activity of the cephalosporins against Gram-positive bacteria, including most *Corynebacteria, Streptococci* and *Staphylococci*, parliculary *Staphylococcus aureus* and *Staphylococcus intermedius*.

The first-generation cephalosporins have activity against Gram-negative, including some *E.coli*, *Klebsilla pneumoniae*, *Haemophilus influenza*, *Proteus mirabilis*, *Actinobacillus*, *Pasteurella* and *Salmonella* however, *Aactinobacter*, *Citrobacter, Enterobacter,* iondol-positive *Proteus* and *Pseudomonas* are resistant.

Many anaerobic bacteria are susceptible to these antibacterials, with the exception of beta-lactam producing bacteroids and *Clostridium difficile.*

Table (18): Summary of cephalosporin antibiotics

1st Generation	2nd Generation	3rd Generation	4th Generation
Oral	**Oral**	**Oral**	**I.V**
Cephalexin (Keflex, others)	Cefuroxime axetil (Ceftin)	Cefixime (Suprax)	Cefepime (Maxipime)
Cephradine (Velosef, Anspor)	Cefaclor (Ceclor)	Cefdinir (Omnicef)	
Cefadroxil (Duricef, Ultracef)	Cefprozil (Cefzil)		
I.V	Ceftibutin (Cedax)	**I.V**	
Cefazolin (Ancef, others)	*Loracarbef (Lorabid)	Ceftazidime (Fortaz, others)	
Cephalothin (Keflin, others)	**I.V**		
Cephapirin (Cefadyl)	Cefamandole (Mandol)	Cefoperazone (Cefobid)	
Cephradine (Velosef)	Cefonocid (Monacid)	Ceftriazone (Rocephin)	
	Cefuroxime (Zinacef)	Cefotaxime (Claforan)	
	Cefoxitin (Mefoxin)	Ceftizoxime (Cefizox)	
	Cefotetan (Cefotan)		
	Cefmetaole (Zefazone)		

Second-generation cephalosporins have the same efficacy as or perhaps slightly less efficacy than first-generation against Gm+ve; however this lack of efficacy is primarily against *S. aureus* and *S. intermedius*. Second generation is more effective than first generation in the treatment of infections caused by Gm-ve bacteria such as *E.coli*, *Klebsiella*, *Enterobacter*, and *Proteus*. Many anaerobic bacteria are susceptible to 2^{nd} generation however *Enterococcus* and *Pseudomonas* species are resistant to 2^{nd} generation.

Use of these antimicrobials is generally reversed for that are resistant to 1^{s}t generation cephalosporins.

Third generation is the most effective of the cephalosporins against antibiotics-resistant Gm-ve bacteria.

Third generation in general are no more and perhaps are less effective than other cephalosporins against gm+ve bacteria Cefotaxim, Ceftazidime, ceftizoxine and Ceftriaxone are the only cephalosporins that consistently reach effective antibacterial concentration in the central nervous system in patients with inflamed meninges.

Foruth generation cephalosporin has a similar to third generation cephalosporins. More resistant to chrosomal beta-lactamase (e.g *Enterobacteriaceae*)

Mechanism of action:-

Cephalosporins are beta-lactam antibiotics that produce their bactericidal effect by inhibition of cell wall synthesis. The site of action for beta-lactam antibiotics is the penicillin-binding proteins (PBPs) on the inner surface of the bacterial cell membrane that are involved in synthesis of the cell wall.

In actively growing cells, the cephalosporins bind to the PBPs within the cell wall and lead to interference in production of cell wall peptidoglycans and subsequent lysis of the cell wall in iso-osmotic environment.

Differences in affinity for the types of PBPs by different beta-lactam and the bacterial defense mechanisms explain the variation in bactericidal activity among cephalosporins.

General Properties:-

The physical and chemical properties of the cephalosporins are similar to those of the penicillins, although the cephalosporins are some what more stable to pH and temperature changes. Cephalosporins are weak acids derived from 7-aminocephalosporanic acid. They are used either as the free base form for PO administration (if acid stable) or as sodium salts in aqueous solution for parenteral delivery (sodium salt of cephalothin contains 2.4 mEq sodium/g). Cephalosporins also contain a β-lactam nucleus that is susceptible to β-lactamase (cephalosporinase) hydrolysis. These β-lactamases may or may not also attack penicillins.

Modifications of the 7-aminocephalosporanic acid nucleus and substitutions on the side chains by semisynthetic means have produced differences among cephalosporins in antibacterial spectra, β-lactamase sensitivities, and pharmacokinetics.

Pharmacokinetic Features

Absorption:

Only a few cephalosporins are acid stable and thus effective when administered orally (cephalexin, cephradine, cefadroxil, and cefaclor). They are usually well absorbed, and bioavailability values are 75-90%. The others

are administered either IV or IM, with peak plasma concentrations occurring ~30 min after injection.

Biotransformation:

Several cephalosporins (such as cephalothin, cephapirin, cephacetrile, and cefotaxime) are actively deacetylated, primarily in the liver but also in other tissues. The deacetylated derivatives are much less active with the exception of ceftiofur. Ceftiofur is metabolized to several active metabolites that can contribute significantly to efficacy. Few of the other cephalosporins are metabolized to any appreciable extent.

Excretion:

Most cephalosporins are excreted by renal tubular secretion, although glomerular filtration is important in some cases (cephaloridine, cephalexin, and cefazolin). In renal failure, dose rates should be reduced. Biliary elimination of the newer cephalosporins (e.g, cefoperazone) may be significant. Generally, these β-lactam antibiotics maintain effective blood levels for only 6-8 hr.

Pharmacokinetic Values:

Plasma half-lives are often 30-120 min, but there are exceptions. Third-generation cephalosporins tend to have longer plasma half-lives in man, but this is not always the case in other animals—substantial species differences exist. Dosage modifications are often required in hepatic and renal disease.

Effects and Toxicity:

The cephalosporins are relatively nontoxic, although cephaloridine may be nephrotoxic in some species. IM injections can be painful, and repeated IV administration may lead to local phlebitis. Nausea, vomiting, and diarrhea may occasionally occur. Hypersensitivity reactions of several forms

have been seen, particularly in animals with a history of acute penicillin allergy. Superinfection may arise with the use of cephalosporins, and *Pseudomonas* or *Candida spp* are likely opportunistic pathogens. Prolonged treatment with cephalosporins in man has been associated with interstitial nephritis, hepatitis, thrombocytopenia, and neutropenia. These drugs should be used with caution in animals with renal disease. Chronic administration of cephaloridine may lead to anemia in cats.

Interactions:

In vitro incompatibilities are quite common for cephalosporin and cephamycin preparations. Potential pharmacokinetic interactions are similar to those of the penicillin group. Aminoglycosides may enhance cephaloridine nephrotoxicity, but there is some doubt about this particular interaction. Furosemide and ethacrynic acid, however, do appear to potentiate the nephrotoxic action of cephaloridine.

Drug Withdrawal and Milk Discard Times:

Although prolonged tissue residues for most cephalosporins are not anticipated, withdrawal times are not available for most of the cephalosporins because they are not approved for use in food animals in most countries.

Therapeutic Indications and Dose Rates

The cost of cephalosporins has limited their use in veterinary medicine. However, first-generation cephalosporins have proven useful, particularly for infections involving *Staphylococcus* (e.g, oral cephalexin for dermatitis) and for surgical prophylaxis (e.g, cefazolin). Ceftiofur is approved for use in bovine respiratory disease principally caused by *Pasteurella spp* and in urinary tract infections in dogs. Use of ceftiofur for treatment of soft-tissue infections in dogs is not recommended because proper dosages and

safety have not been documented for this use. Cephalosporins are particularly useful for treating infections of soft tissue and bone due to bacteria that are resistant to other commonly used antibiotics. Because of their favorable pharmacokinetic characteristics and effectiveness, they are often administered I.V, 1 hr before surgery. Because of their ability to penetrate tissues and fluids so readily (the CSF being an exception for most), they are often effective in the management of osteomyelitis, prostatitis, and arthritis. Oral cephalosporins are also usually effective in the management of urinary tract infections, except those due to *Pseudomonas aeruginosa*. Cephapirin benzathine is used for dry-cow therapy, and cephapirin sodium is used in treatment of mastitis. The dose rate and frequency should be adjusted as needed for the individual.

IV. OTHER β-LACTAM ANTIBIOTICS

A. Carbapenems

Carbapenems are synthetic β-lactam antibiotics that differ from the penicillins in that the sulfur atom of the thiazolidine ring has been externalized and replaced by a carbon atom Imipenem and meropenem are the only drugs of this group currently available.

1. **Antibacterial spectrum:** Imipenem and meropenem are the broadest-spectrum. Imipenem resists hydrolysis by most β- role in empiric therapy, because it is active against penicillinase-producing Gram-positive and Gram-negative organisms, anaerobes, and *Pseudomonas aeruginosa* (although other pseudomonas strains are resistant, and resistant strains of *P. aeruginosa* have been reported to arise during therapy). Meropenem has antibacterial activity similar to that of imipenem.

2. **Pharmacokinetics:** Imipenem and meropenem are administered I.V, and penetrate well into body tissues and fluids, including the CSF when the meninges are inflamed. They are excreted by glomerular filtration. Imipenem undergoes cleavage by a dehydropeptidase found in the brush border of the proximal renal tubule. This enzyme forms an inactive metabolite that is potentially nephrotoxic. Compounding the imipenem with cilastatin protects the parent drug and, thus, prevents the formation of the toxic metabolite. This allows the drug to be used in the treatment of urinary tract infections. Meropenem does not undergo metabolism.

3. Therapeutic uses:

1) Complicated skin & soft tissue infections.
2) Pneunomia.
3) Complicated urinary tract infection. 4) Active pelvic infection.

B. Monobactams

The monobactams, which also disrupt bacterial cell wall synthesis, are unique, because the β-lactam ring is not fused to another ring. Aztreonam which is the only has antimicrobial activity directed primarily against the *Enterobacteriaceae*, but it also acts against aerobic Gram-negative rods, including P. *Aztreonam* is resistant to the action of β-lactamases. It is administered either IV or IM, and is excreted in the urine. It can accumulate in patients with renal failure. *Aztreonam* is relatively nontoxic, but it may cause phlebitis, skin rash, and occasionally, abnormal liver function tests. This drug has a low immunogenic potential, and it shows little cross-reactivity with antibodies induced by other β-lactams. Thus, this drug may offer a safe alternative for treating patients who are allergic to penicillins and/or cephalosporins. Therapeutically, aztreonam is used in urinary tract infection, Gm–ve bacteremia.

V. β-LACTAMASE INHIBITORS

Hydrolysis of the β-lactam ring, either by enzymatic cleavage with a β-lactamase or by acid, destroys the antimicrobial activity of a β-lactam antibiotic. β-Lactamase inhibitors, such as clavulanic acid and *tazobactam* contain a β-lactam ring but, by themselves, do not have significant antibacterial activity. Instead, they bind to and inactivate β-lactamases, thereby protecting the antibiotics that are normally substrates for these enzymes. The β-lactamase inhibitors are therefore formulated with β-lactamase-sensitive antibiotics. For example, the effect of *clavulanic acid* and *amoxicillin* on the growth of β-lactamase-producing *E. coli*. *Clavulanic acid* alone is nearly devoid of antibacterial activity.

VI. OTHER AGENTS AFFECTING THE CELL WALL

1. **Bacitracin**: It is obltained from *B. Subtilis*. It is similar to streptomycin as it is not absorbed from GIT. The mode of action appears to be interference with cell wall formation. It is effective against Gm +ve cocci and some spirochaetes. It is mainly used as food additive for promotion of growth in poultry.

2. **Vancomycin** is a tricyclic glycopeptide that has become increasingly important because of its effectiveness against multiple drug-resistant organisms, such as *Enterococci.*

   A. Mode of action

   Vancomycin inhibits synthesis of bacterial cell wall phospholipids as well as peptidoglycan polymerization by binding to the D-Ala-D-Ala side chain of the precursor pentapeptide. This prevents the transglycosylation step in peptidoglycan polymerization, thus weakening the cell wall and damaging the underlying cell membrane.

   B. Antibacterial spectrum

   Vancomycin is effective primarily against gram-positive organisms specially *staphylococci*, *streptococci* and *enterococci*. Vancomycin is used for treatment of infection of sensitive bacteria. Bacitracin is manily used as food additive for promotion of growth in poultry.

3. **Novobiocin:** It is a bacteriostatic antibiotic related chemically to dicoumaral. It acts like benzylpenicillin by interfering with the bacterial cell wall synthesis. It is used for the treatment of *streptococcal* and *staphylococcal* infections, anthrax and mastitis. It is prepared for intramammary injection at a dosage of 250 mg/ infected quarter.

C- PROTEIN SYNTHESIS INHIBITORS

I. OVERVIEW

A number of antibiotics exert their antimicrobial effects by targeting the bacterial ribosome, which has components that differ structurally from those of the mammalian cytoplasmic ribosome. In general, the bacterial ribosome is smaller (70S) than the mammalian ribosome (80S), and is composed of 50S and 30S subunits (as compared to 60S and 40S sub-units). The mammalian mitochondrial ribosome, however, more closely resembles the bacterial ribosome. Thus, although drugs that interact with the bacterial target usually spare the host cells, high levels of drugs such as *chloramphenicol* or the tetracyclines may cause toxic effects as a result of interaction with the mitochondrial ribosomes. Figure (47) lists the drugs which inhibitis protein synthesis.

II. TETRACYCLINES

The tetracyclines are a group of closely related compounds that, as the name implies, consist of four fused rings with a system of conjugated double bonds. Substitutions on these rings are responsible for a variation in the drugs individual pharmacokinetics, which cause small differences in their clinical efficacy.

A. Mechanism of action

Entry of these agents into susceptible organisms is mediated both by passive diffusion and by an energy-dependent transport protein : mechanism unique to the bacterial inner cytoplasmic membrane. Nonresistant strains concentrate the tetracyclines intracellularly. The drug binds reversibly to the 30S subunit of the bacterial ribosome, thereby blocking access of the amino

acyl-tRNA to the mRNA-ribosome complex at the acceptor site. By this mechanism, bacterial protein synthesis is inhibited (Figure 48)

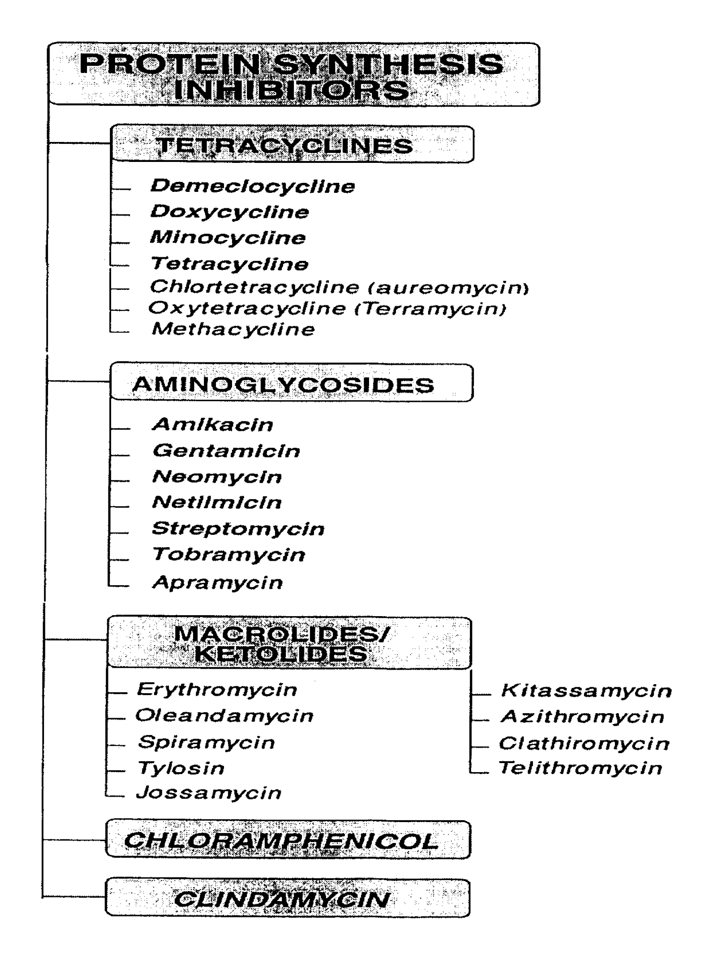


Figure (47): Summary of protein synthesis inhibitors

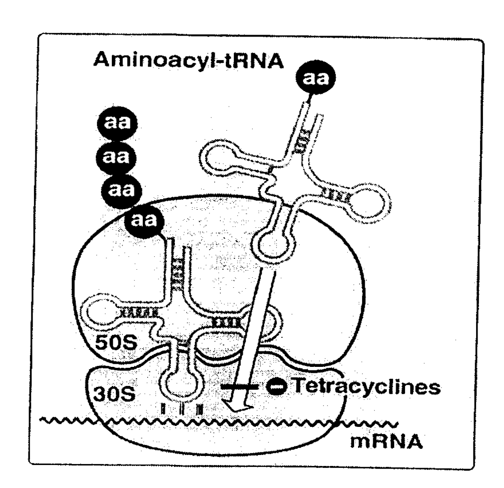


Figure (48): Tetracyclines bind to 30S ribosomal subunit, thus preventing the aminoacyl-t-RNA to the ribosome. aa = amino acid.

B. Antibacterial spectrum

As broad-spectrum, bacteriostatic antibiotics, the tetracyclines are effective against Gram-positive and Gram-negative bacteria as well as against organisms other than bacteria as rickettiea, some protozoa and mycoplasma.

C. Resistance

Widespread resistance to the tetracyclines limits their clinical use. The most commonly encountered, naturally occurring resistance ("R") factor confers an inability of the organism to accumulate the drug, thus producing resistance. This is accomplished by Mg^{2+}-dependent, active efflux of the drug, mediated by the plasmid-encoded resistance protein (TetA). Other less important mechanisms of bacterial resistance to tetracyclines include enzymatic inactivation of the drug, and production of bacterial proteins that

prevent tetracyclines from binding to the ribosome. Any organism resistant to one tetracycline is resistant to all. The majority of penicillinase-producing.; *staphylococci* are now insensitive to tetracyclines.

D. Pharmacokinetics

1. **Absorption:** All tetracyclines are adequately but incompletely absorbed after oral ingestion. However, taking these drugs concomitantly with dairy foods in the diet decreases absorption due to the formation of nonabsorbable chelates of the tetracyclines with calcium ions. Non absorbable chelates are also formed with other divalent and trivalent cations (for example, those found in magnesium and aluminum antacids and in iron preparations). *Doxycycline* and *minocycline* are almost totally absorbed on oral administration. *Doxycycline* is preferred for parenteral administration.

2. **Distribution**: The tetracyclines concentrate in the liver, kidney, spleen, and skin, and they bind to tissues undergoing calcification (for example, teeth and bones) or to tumors that have a high calcium content (for example, gastric carcinoma). Penetration into most body fluids is adequate. Although all tetracyclines enter the cerebrospinal fluid (CSF), levels are insufficient for therapeutic efficacy, except for *minocycline. Minocycline* enters the brain in the absence of inflammation and also appears in tears and saliva. All tetracyclines cross the placental barrier, and concentrate in fetal.bpnes and dentition.

3. **Blood level:** 2-4 μg/ml (chlortera cycline) and 0.5 μg/ml (oxytetracycline) are considered to be therapeutically effective.

4. **Fate**: All the tetracyclines concentrate in the liver, where they are, in part, metabolized and conjugated to form soluble glucuronides. The parent drug and/or its metabolites are secreted into the bile. Most tetracyclines

are reabsorbed in the intestine via the entero-hepatic circulation and enter the urine by glomerular filtration. Unlike other tetracyclines, *doxycycline* can be employed for treating infections in renally compromised patients, because it is preferentially excreted via the bile into the feces. Tetracyclines are also excreted in breast milk.

E. Adverse effects

1. **Gastric discomfort**: Epigastric distress commonly results from irritation of the gastric mucosa and is often responsible for noncompliance in patients treated with these drugs. The discomfort can be controlled if the drug is taken with foods other than dairy products.
2. **Effects on calcified tissues:** Deposition in the bone and primary dentition occurs during calcification in growing. This causes discoloration and hypoplasia of the teeth and a temporary stunting of growth.
3. **Fatal hepatotoxicity:** This side effect has been known to occur in pregnant female who received high doses of tetracyclines.
4. **Diarrhea**: may be occur due to suppression of the normal flora of intestine and allow resistant strains of bacteria, mould and fungi to grow.

F. Therapeutic uses: tetracyclines are used for treatment of mastitis, strangles, anthrax, pasteurellosis, leptospirosis, salmonellosis, infectious sinusitis in turkeys & chronic respiratory disease in chicken. Also it can be used for treatment of non-specific infections as hepaltitis, metritis, pneumonia, tonsillitis, bronchitis and cystitis.

Chlortetracycline has been used as ointement for eye infections, otitis externa, burns, wounds, abscesses and other forms of pyogenic infections.

Dose:

Aureomycin: 20-50 mg/kg daily orally.

Terramycin: 10 mg/kg (S.A.), 20 mg/kg (L.A.)

Tetracycline: 5-10 mg/kg.

III. AMINOGLYCOSIDES

Aminoglycosides include streptomycin, neomycin, kanamycin, gentamicin, netilmicin, topramycin, apramycin and amikacin.

Aminoglycoside antibiotics had been the mainstays for treatment of serious infections due to aerobic Gram-negative bacilli. However, because their use is associated with serious toxicities, they have been replaced to some externt by safer antibiotics, such as the third-generation cephalosporins and the fluoroquinolones. Aminoglycosides that are derived from *Streptomyces* have -mycin suffixes, whereas those derived from *Micromonospora* end in -micin. The terms "aminoglycoside" and "aminocyclitol" stem from their structure— two amino sugars joined by a glycosidic linkage to a central hexose (aminocyclitol) nucleus. Their polycationic nature precludes their easy passage across tissue membranes. All members of this family are believed to inhibit bacterial protein synthesis by the mechanism determined for streptomycin. Streptomycin is obtained from *Streptomyces griseus*. Neomycin is obtained from *Streptomyces fradiae* as described below.

A. Mechanism of action

Susceptible Gram-negative organisms allow aminoglycosides to diffuse through porin channels in their outer membranes. These organisms also have an oxygen-dependent system that transports the drug across the cell membrane. The antibiotic then binds to the 30S subunit prior to ribosome formation (Figure 49). There, it interferes with assembly of the functional ribosomal apparatus, and/or can cause the 30S subunit of the completed

ribosome to misread the genetic code, Polysomes become depleted, because the aminoglycosides interrupt the process of polysome disaggregation and assembly.

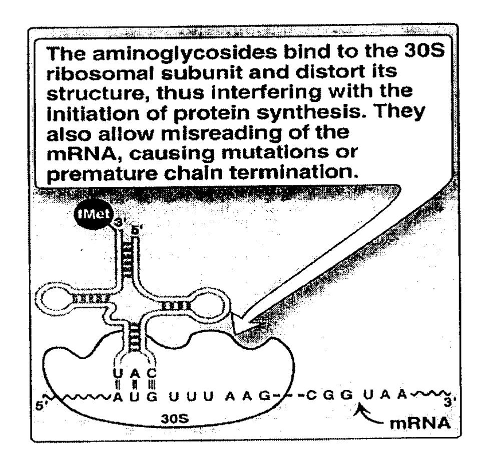


Figure (49): Mechanism of action of aminoglycosides

B. Antibacterial spectrum

The aminoglycosides are effective in the empirical treatment of infections suspected of being due to aerobic Gram-negative bacilli, including *Pseudomonas aerugingsa.* To achieve an additive or synergistic effect, aminoglycosides are often combined with a β-lactam antibiotic, or *vancomycin,* or a drug active against anaerobic bacteria. All aminoglycosides are bactericidal. The exact mechanism of their lethality is unknown, because other antibiotics that affect protein synthesis are generally bacteriostatic. The aminoglycosides are only effective against aerobic organisms, because strict

anaerobes lack the oxygen-requiring transport system. Streptomycin is highly effective against *Mycobacterium tuberculosis.*

C. Resistance

Resistance can be caused by 1) decreased uptake of drug when the oxygen-dependent transport system for aminoglycosides or porin channels are absent, 2) an altered 30S ribosomal subunit aminoglycoside-binding site that has a decreased affinity for the drugs, or 3) plasmid-associated synthesis of enzymes (for example, acetyl transferases, nucleotidyl transferases, and phosphor transferases) that modify and inactivate aminoglycoside antibiotics. Each of these enzymes has its own aminoglycoside specificity; therefore, cross-resistance is not an invariable rule. *Netilmicin* and *amikacin are* less vulnerable to these enzymes than are the other antibiotics of this group.

D. Pharmacokinetics

1. **Administration:** The highly polar, polycationic structure of the aminoglycosides prevents adequate absorption after oral administration. Therefore, all aminoglycosides (except *neomycin* must be given parenterally to achieve adequate serum levels. The bactericidal effect is concentration and time dependent; that is, the greater the concentration of drug, the greater the rate at which the organisms die. They also have a postantibiotic effect. Because of these properties, once-daily dosing with the aminoglycosides can be employed. This results in fewer toxicities and is cheaper to administer. The exceptions are pregnancy, neonatal infections, and bacterial endocarditis, in which these agents are administered in divided doses every eight hours.

2. **Blood level**: 5μg/ml is satisfactory.

3. Distribution: All the aminoglycosides have similar pharmacokinetic properties. Levels achieved in most tissues are low, and penetration into most body fluids is variable. Concentrations in CSF are inadequate, even when the meninges are inflamed. Except for *neomycin*, the aminoglycosides may be administered intrathecally or intraventricularly. High concentrations accumulate in the renal cortex and in the endolymph and perilymph of the inner ear, which may account for their nephrotoxic and ototoxic potential. All aminoglycosides cross the placental barrier and may accumulate in fetal plasma and amniotic fluid.

4. Fate: Metabolism of the aminoglycosides does not occur in the host. All are rapidly excreted into the urine, predominantly by glomerular filtration. Accumulation occurs in patients with renal failure and requires dose modification. Also it is excreted in milk in desirable and effective quantities.

E. Adverse effects

It is important to monitor plasma levels of *gentamicin, tobramycin, netilmicin,* and *amikacin* to avoid concentrations that cause dose-related toxicities. [When the drugs are administered two to three times daily, both peak and trough levels are measured]. Peak levels are defined as those obtained thirty minutes to one hour after infusion. Trough levels are obtained immediately before the next dose. When once-daily dosing is employed, only the trough concentrations are monitored. Patient factors, such as old age, previous exposure to aminoglycosides, gender, and liver disease, tend to predispose patients to adverse reactions. The elderly are particularly susceptible to nephrotoxicity and ototoxicity.

1. **Ototoxicity**: Ototoxicity (vestibular and cochlear) is directly related to high peak plasma levels and the duration of treatment. The antibiotic accumulates in the endolymph and perilymph of the inner ear, and

toxicity correlates with the number of destroyed hair cells in the organ of Corti. Deafness may be irreversible and has been known to affect fetuses in utero. Patients simultaneously receiving another ototoxic drug, such as the loop diuretics *furosemide, bumetanide,* or *ethacrynic acid* or cisplatin, are particularly at risk. Vertigo and loss of balance (especially in patients receiving streptomycin) may also occur, because these drugs affect the vestibular apparatus.

2. **Nephrotoxicity:** Retention of the aminoglycosides by the proximal tubular cells disrupts calcium-mediated transport processes, and this results in kidney damage ranging from mild, reversible renal impairment to severe, acute tubular necrosis, which can be irreversible.

3. **Neuromuscular paralysis:** The mechanism responsible is a decrease in both the release of acetylcholine from prejunctional nerve endings and the sensitivity of the postsynaptic site.

4. **Allergic reactions:** Contact dermatitis is a common reaction to topically applied neomycin.

F. therapeutic uses:

a) Streptomycin:

1- Bovine mastitis due to Gm –ve bacteria.

2- Vibriosis.

3- Parteurella infections.

4- Leptospirosis in pigs and dogs.

5- Coliform – Salmonella group infections in foals, calves & pigs.

6- Corynebacterium equi infections.

7- Non-specific systemic diseases as cystitis in dogs and gastroenteritis.

Dose:

Dog and cat: 10-20 mg/kg.

Horse, cow, sheep: 10 mg/kg.

Chicken: 2.5-5.0 mg twice daily.

b) Neomycin:

1- Enteritis in calves and foals.

2- Bovine mastitis due to Gm –ve bacteria

c) Gentamicin:

1- For treatment of infection caused by Gm–ve bacteria specially *pseudomonas* and *proteus*.

2- For treatment of eye and ear infection in dogs by topical applications.

d) Tobramycin:

It is used in combination with pencillin for *pseudomonas* infections.

e) Amikacin:

It is used therapeutically as streptomycin.

f) Apramycin:

It is used for Gm–ve intestinal infections and mycoplasmosis as well as colibacillosis in poultry.

IV. MACROLIDES

The macrolides are a group of antibiotics with a macrocyclic lactone structure to which one or more deoxy sugars are attached. *Erythromycin* was the first of these drugs to find clinical application, both as a drug of first choice, and as an alternative to *penicillin* in individuals who are allergic to β-lactam antibiotics. The newer members of this family, (a methylated form of *erythromycin)* and *azithromycin* (having a larger lactone ring), have some features in common with, and others that improve on, *erythromycin*. *Telithromycin*— an *erythromycin* derivative (a ketolide) — has recently been approved. Oleandomycin, spiramycin, tylosin, jossamycin and kitassamycin are also mbmers of macrolides.

A. Mechanism of action:

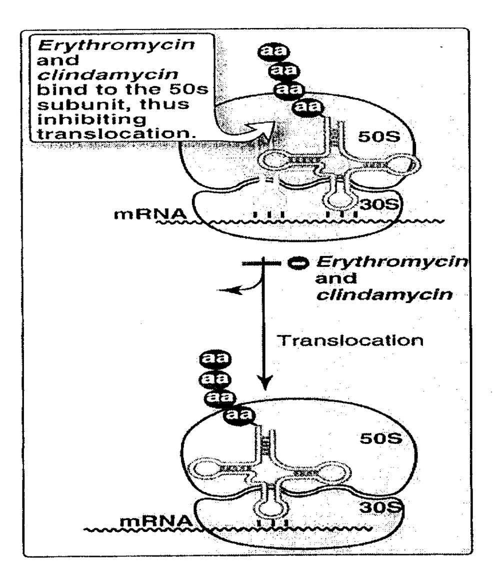


Figure (50): Mechanism of action of erythromycin and clindamycin

The macrolides bind irreversibly to a site on the 50S subunit of the bacterial ribosome, thus inhibiting the translocation steps of protein synthesis (Figure 50). They may also interfere at other steps, such as transpeptidation. Generally considered to be bacteriostatic, they may be cidal at higher doses. Their binding site is either identical or in close proximity to that for clindamycin and chloramphenicol.

B. Antibacterial spectrum

1. **Erythromycin:** This drug is effective against many of the same organisms as *penicillin G*; therefore, it is used in patients allergic to the penicillins.
2. **Oleandomycin**, spiramycin are similar to pencillin in their antibacterial activity.
3. **Tylosin, jossamycin and kitassamycin** are active against Gm +ve and some Gm –ve organism and *mycoplasma.*
4. **Clarithromycin**: This antibiotic has a spectrum of antibacterial activity similar to that of erythromycin, but it is also effective against *Haemophilus influenzae*.
5. **Azithromycin**: Although less active against *streptococci* and *staphylococci* than erythromycin, azithromycin is far more active against respiratory infections due to *H. influenzae.*
6. **Telithromycin**: This drug has an antibacterial spectrum similar to that of azithromycin.

C. Resistance

Resistance to erythromycin is becoming a serious clinical problem. For example, most strains of *staphylococci* in field isolates are resistant to this drug. Several mechanisms have been identified: 1) the inability of the organism to take up the antibiotic or the presence of an efflux pump, both of which limit the amount of intracellular drug; 2) a decreased affinity of the 50S ribosomal subunit for the antibiotic, resulting from the methylation of an adenine in the 23S bacterial ribosomal RNA; and 3) the presence of a plasmid-associated erythromycin esterase.

D. Pharmacokinetics

1. **Administration**: The erythromycin base is destroyed by gastric acid. Thus, either enteric-coated tablets or esterified forms of the antibiotic are administered. All are adequately absorbed on oral administration. Food interferes with the absorption of erythromycin and azithromycin but can increase that of clarithromycin.

2. **Distribution**: Erythromycin distributes well to all body fluids except the CSF. It is one of the few antibiotics that diffuses into prostatic fluid, and it has the unique characteristic of accumulating in macrophages. All concentrate in the liver.

3. **Fate**: Erythromycin and telithromycin are extensively metabolized, and are known to inhibit the oxidation of a number of drugs through their interaction with the cytochrome P450 system

4. **Excretion**: Erythromycin primarily concetreated and excreted in an active form in the bile. Partial reabsorption occurs through the enterohepatic circulation. Inactive metabolites are excreted into the urine.

E. Therapeutic uses:

Members of macrolide antibiotics are used for treatment of infections as penicillin as well as mycoplasmosis in poultry. Jossamycin is used for treatment of CRD, colibacillosis and salmonellosis.

Dose:

Erythromycin:

Cattle, horse dog, cat: 4-8 mg/kg every 12 hours.

Poultry and turkeys: 1/10000 parts of darinking water for 4-5 i.m. daily. Tylosin: 2-10 mg/kg i.m. daily.

V. CHLORAMPHENICOL

Chloramphenicol is active against a wide range of Gram-positive and Gram-negative organisms. However, because of its toxicity, its use is restricted to life-threatening infections for which no alternatives exist. Chloramphenicol is obtained from *Streptomyces venezuelae*.

A. Mechanism of action

The drug binds to the bacterial 50S ribosomal subunit and inhibits protein synthesis at the peptidyl transferase reaction (Figure 51). Because of the similarity of mammalian mitochondrial ribosomes to those of bacteria, protein synthesis in these organelles may be inhibited at high circulating chloramphenicol levels, producing bone marrow toxicity.

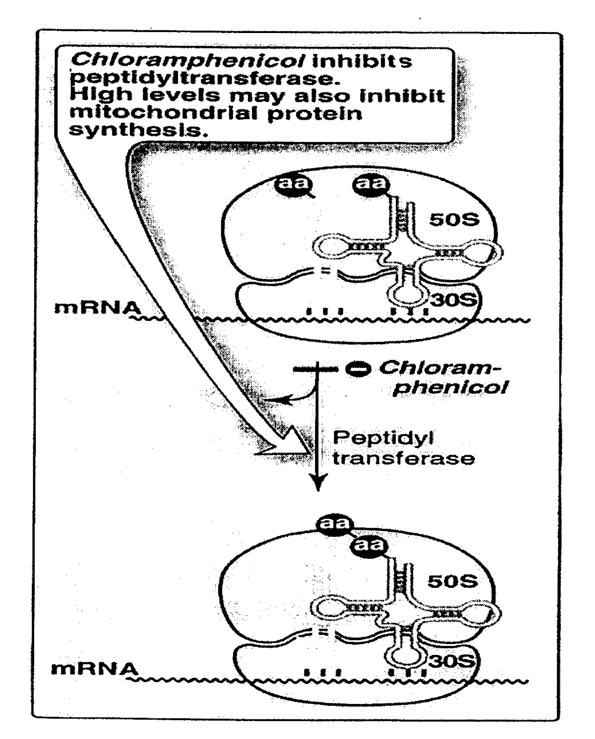


Figure (51): Mechanism of action of chloramphenicol

B. Antimicrobial spectrum

Chloramphenicol, a broad-spectrum antibiotic, is active not only against bacteria but also against other microorganisms, such as rickettsiae. *Pseudomonas aeruginosa* is not affected, nor are the *chlamydiae.* Chloramphenicol has excellent activity against anaerobes. The drug is either bactericidal or (more commonly) bacteriostatic, depending on the organism.

C. Resistance

Resistance is conferred by the presence of an R factor that codes for an acetyl coenzyme A transferase. This enzyme inactivates chloramphenicol. Another mechanism for resistance is associated with an inability of the antibiotic to penetrate the organism. This change in permeability may be the basis of multidrug resistance.

D. Pharmacokinetics

Chloramphenicol may be administered either intravenously or orally. It is completely absorbed via the oral route because of its lipophilic nature, and is widely distributed throughout the body. It readily enters the normal CSF. The drug inhibits the hepatic mixed-function oxidases. Excretion of the drug depends on its conversion in the liver to a glucuronide, which is then secreted by the renal tubule. Only about ten percent of the parent compound is excreted by glomerular filtration. Chloramphenicol is also secreted into milk of female.

E. Adverse effects

The clinical use of chloramphenicol is limited to life-threatening infections because of the serious adverse effects associated with its administration. In addition to gastrointestinal upsets, overgrowth of *Candida albicans* may appear on mucous membranes.

1. **Anemias:** Hemolytic anemia occurs in patients with low levels of glucose 6-phosphate dehydrogenase. Other types of anemia occurring as a side effect of chloramphenicol include reversible anemia, which is apparently dose-related and occurs concomitantly with therapy, and aplastic anemia, which although rare is idiosyncratic and usually fatal. Aplastic anemia is independent of dose and may occur after therapy has ceased.

2. **Interactions:** Chloramphenicol is able to inhibit some of the hepatic mixed-function oxidases and, thus, blocks the metabolism of such drugs as warfarin, phenytoin and tolbutamide, thereby elevating their concentrations and potentiating their effect.

F. Therapeutic uses:

Chloramphenicol is used for treatment of salmonella infection, cell diphtheria, virus pneumonia and locally in treatment of infections bovine keratitis, wound pyogenic infection and external otitis. In uman, the use of chloramphenicol must be resticted for the treatment of typhoid.

Dose:

150 mg/kg divided 3 doses daily in large animals

2-4 mg/kg i.v. daily.

1% ointment, locally.

VI. CLINDAMYCIN

Clindamycin has a mechanism of action that is the same as that of erythromycin. Clindamycin is employed primarily in the treatment of infections caused by anaerobic bacteria. It is also significantly active against non-enterococcal, Gram-positive cocci. Resistance mechanisms are the same as those for erythromycin, but cross-resistance is not a problem. Clindamycin is well absorbed by the oral route. It distributes well into all body fluids except the CSF. Adequate levels of Clindamycin are not achieved in the brain, even when meninges are inflamed. Penetration into bone occurs even in the absence of inflammation. Clindamycin undergoes extensive oxidative metabolism to inactive products. The drug is excreted into the bile or urine by glomerular filtration, but thera-peutically effective levels of the parent drug are not achieved in the urine.

D. INHILITORS OF NUCLEIC ACID FUNCTION OR SYNTHESIS

Members of this group are illustrated in Figure (52).

1. FLUOROQUINOLONES:

The fluoroquinolones consist of a carboxyl group, fluorine atom and piperazine ring attached to a quinoline ring. They are weak acids and are lipophilic. Water solubule salts are used in parenteal preparations.

Classification:

Fluoroquinolones are classified according to its nature into:

1- **First generation:** e.g. oxolinic acid,. flumiquine and nalidixic acid which is used less after today, has moderate Gram negative activity. It achieves minimal serum concentrations and is restricted to the treatment of uncomplicated urinary tract infections. It acts mainly on gram –ve rods.

2- **Second generation:** e.g. enrofloxcin, aprofloxacin, norfloxacin and ofloxacin. Members of the second generation have expanded Gram negative rods activity and also have some activity aganest Gram – positive *cocci*, *Mycoplasma pneumonia* and *Chlamydia pneunoniae*.

3- **Third generation:** e.g. gatifloxacin, levofloxacin, moxifilaxacin and sparfloxacin. Members of the third generation retain expanded gram negative rods and show improved activity against.

4- **Fourth generation**: e.g. trovaflaxcin which shows improved Gram +ve cocci, gram +ve bacilli, Gram –ve rods and anaerobic organisms.

Mechanism of action:

The fluoroquinolones inhibit bacterial DNA gyrase, an enzyme that control DNA gyrase, an enzyme that controls DNA supercoiling as the

replicating strands separate. Inhibition of gyrase results in degradation of chromosomal DNA at the replicating site. Fluoroquinolones are bactericidal.

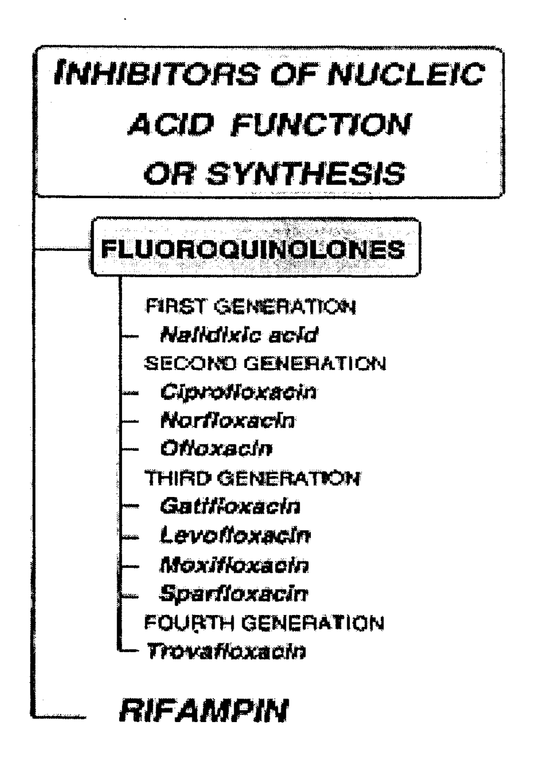


Figure (52): Summary of antibacterials affecting nucleic acid function and synthesis.

Pharmacokinetics:

Oral absosption of fluoroquinolones is rapid e.g. dogs achieve peak plasma concentration one hour after administration. Distribution of fluoroquinolones is very well into all tissues and body fluids. Both the parent

drug and metabolites are excreted in urine and bile. Renal tubular active secretion results in high urinary concentrations.

Bacterial resistance:

Development of bacterial resistance is relatively rare. Extended exposure to therapeutic dosages may lead to the appearance of mutants that resist fluoroquinolone binding to DNA gyrase.

Adverse effects include erosion of articular cartilage in young dogs. Flouorquinolones should not be administesed to small and medium breeds for the first 8 months and large breeds for the first 18 months of life.

Therapeutic use:

1- Urinary tract infections: due to *E-coli, staphylococcus spp, streptococcus spp* and less common due to *proteus, pseudomonas aeruginosa.*

2- Respiratory tract infections due to Gram + ve, Gram –ve and mycoplasma.

3- Gastrointestinal tract infections due to *E-coli, enterococcus, staphycoccous aureaus* and *pseudomonas aeruginosa.*

Table (19): Indications of use and formulations of quinolones for treatment of infection in animals

Animal species	Licensed use	Major bacteria	Formulations
Cattle	Respiratory, enteric	*Pasteurella* spp., *Haemophilus somnus, Mycoplasma bovis*	Injectable, bolus
Broilers	Respiratory, enteric	*E. coli, Mycoplasma, Pasteurella, Salmonella*	Oral (water medication)
Turkeys	Respiratory, enteric	*E. coli, Mycoplasma, Pasteurella, Salmonella*	Oral (water medication)
Fish	Generalized conditions (septicemia), skin/ulcers	*Aeromonas hydrophila Vibrio* spp.	Oral (feed medication), Water bath
Swine	Respiratory, enteric, mastitis/metritis	*Pasteurella* spp., *Actinobacillus pleuropneumoniae, Mycoplasma, E. coli*	Injectable, oral solution, feed medication
Dogs	Skins/wounds, urinary tract, respiratory	*S. inter medius, E. coli, Pasteurella*	Tablets, injectable
Cats	Skins/wounds, urinary tract, respiratory	*S. intermedius, E. coli, Pasteurella*	Tablets, injectable

2. **RIFAMPIN**: Rifampin which is derived from the soil mold *Streptomyces,* found application in the treatment of a number of different bacterial infections. Because resistant strains rapidly emerge during therapy, it is never given as a single agent in the treatment of active tuberculosis.

1. **Mechanism of action:** Rifampin blocks transcription by interacting with the β subunit of bacterial but not human DNA-dependent RNA polymerase. Rifampin inhibits RNA synthesis by suppressing the initiation step.

2. **Antimicrobial spectrum:** Rifampin is bactericidal for both intracellular and extracellular mycobacteria, including *M. tuberculosis*, and atypical *mycobacteria*, such as *M. kansasis*. It is effective against many Gram-positive and Gram-negative organisms, and is frequently used prophylactically for individuals exposed to meningitis caused by *meningococci* or *Haemophilus influenzae.* **Rifabutin**, an analog of *rifampin,* has some activity against *Mycobacterium avium-intracellulare* complex but is less active against tuberculosis.

3. **Resistance**: Resistance to *rifampin* can be caused by a mutation in the affinity of the bacterial DNA-dependent RNA polymerase for the drug or by decreased permeability.

4. **Pharmacokinetics**: Absorption is adequate after oral administration. Distribution of *rifampin* occurs to all body fluids and organs. Adequate levels are attained in the CSF even in the absence of inflammation. The drug is taken up by the liver and undergoes enterohepatic cycling. *Rifampin* itself can induce the hepatic mixed-function oxidases, leading to a shortened half-life. Elimination of metabolites and the parent drug is via the bile into the feces or via the urine.

D. PYRAZINAMIDE

Pyrazinamide is a synthetic, orally effective, bactericidal, antitubercualr agent used in combination with isoniazid and rifampin. It is bactericidal to activily dividing orgnasims.

3. LINCOMYCIN

It is a bacteristatic antibiotic closely related to cephalosporins, acting by interfring with DNA synthesis in the bacterial cell. It is effective only on Gm +ve bacteria. It is absorbed after oral administration and enters all the tissues placenta and bone. It is found in milk and bile, but it does not pass to the blood – brain barrier.

It is used for treatment of mycoplasmosis, Gm +ve infections porticuraly those caused by *streptococci* and *staphylococci*. It has a cross resistance only with erythromycin.

Dose:

20 mg/kg orally every 12 hours.

E. INHIBITORS OF CELL MEMBRANE FUNCTION

1. ISONIAZID

Isoniazid is a synthetic analogue of pyridoxine. It is the most potent of the antitubercular drugs, but is never given as a single agent in the treatment of active tuberculosis,

1. **Mechanism of action:** Isoniazid is a pro-drug that is activated by a mycobacterial catalase-peroxidase (KatG). Genetic and biochemical evidence has implicated at least two different target enzymes for isoniazid within the unique Type II fatty acid synthase system involved in the production of mycolic acids. Mycolic acid is a unique class of very-long-chain, (3-hydroxylated fatty acid found in rnycobacterial cell walls. Decreased mycolic acid synthesis corresponds with the loss of acid-fastness after exposure to isoniazid. The targeted enzymes are enoyl acyl carrier protein reductase (InhA) and a β-ketoacyl-ACP synthase (KasA). The activated drug binds to and inhibits these enzymes, which are essential for the synthesis of mycolic acid.

2. **Antibacterial spectrum**: For bacilli in the stationary phase, isoniazid is bacteriostatic, but for rapidly dividing organisms. It is bactericidal and effective against intracellular bacteria. Isoniazid is specific for treatment of *M. tuborculosis.*

3. **Pharmacokinetics:** Orally administered isoniazid readily absorbed. Absorption is impaired if isoniazid taken with food, particularly car-bohydrates, or with aluminum-containing antacids. The drug diffuses into all body fluids, cells, and caseous material (necrotic tissue resembling cheese that is produced in tubercles). Drug levels in the cerebrospinal fluid (CSF) are about the same as those in the serum. The drug readily penetrates host cells and is effective against bacilli growing

intracellularly. Infected tissue tends to retain the drug longer. Isoniazid undergoes N-acetylation and hydrolysis, resulting in inactive products.

2. AMPHOTERICIN B

Amphotericin B. is a naturally occurring, polyene macrolide antibiotic produced by Streptomyces nodosus. In spite of its toxic potential, amphotericin B is the drug of choice for the treatment of life-threatening, systemic mycoses.

1. **Mechanism of action:** Several amphotericin B molecules bind to ergosterol in the plasma membranes of sensitive fungal cells. There, they form pores (channels) that require hydrophobic interactions between the lipophilic segment of the polyene antibiotic and the sterol (Figure 54). The pores disrupt membrane function, allowing electrolytes (particularly potassium) and small molecules to leak from the cell, resulting in cell death.

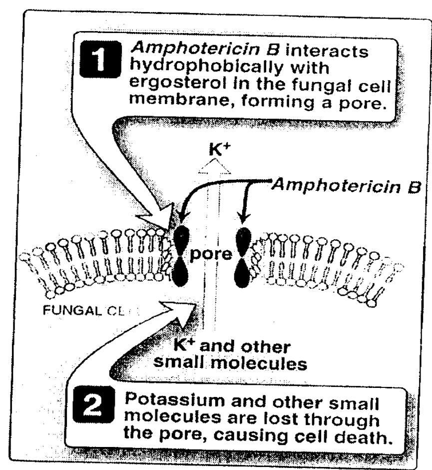


Figure (54): Model of a pore formed by amphotericin B in the lipid bilayer membrane.

2. **Antifungal spectrum:** Amphotericin B is either fungicidal or fungistatic, depending on the organism and the concentration of the drug. It is effective against a wide range of fungi, including *Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans, Blastomyces dermatitidis* and many strains of *Aspergillus.*

3. **Resistance:** Fungal resistance, although infrequent, is associated with decreased ergosterol content of the fungal membrane.

Therapeutic uses:

Amphotericin B is used for treatment of mycotic infections caused by fungi sensistive to the drug.

3. POLYMYXINS B & E (COLISTIN)

Polymyxins are polypeptide antibiotics water soluble and stable. It is not absorbed from the intestine, so it is used locally and in urinary infection caused by bacteria sensitive to polymyxin B.

Mechanism of action;

Polymyxin is bactericidal which acting on the growing and non-growing cells. It acts by strong binding to bacteria increasing the permeability of its cell membrane, so releasing its cytoplasmic solutes. It also inhibits the bacterial oxidative mechanism.

Antibacterial spectrum;

Polymyxins B and E are narrow spectrum antibiotics with an activity limited to Gm. -ve bacteria, *proteus* and *pseudomonas spp.*

Clinical applications;

1. Bovine mastitis due to *Ps. aeruginosa.*

2. Semen additive; Polymyxin has been used in bull's semen which contained *Pseddomonas* organisms (50 ug/ml diulent).

3. Canine otitis; it is used locally.

4. Enteritis due to *E. coli*,

Dose: 40 000 unit/kg orally.

XV.II. ANTIMYCOTIC DRUGS

Antimycotic drugs are classified according to chemical structure into

1- Organic acids and their salts:

A. Benzoic acid:

In cutaneous fungus infections, benzoic acid (6 %) is combined with salicylic acid (3 %) to make Whitfield's ointment. This is effective against Trichophyton infection in cattle.

B. Salicylic acid:

It has a keratolytic effect which combine with some fungistatic activity [illegible] suitable for treatment of ringworm.

Undecylenic acid:

This is effective topical fungistatic agent especially against *Microsporum* species. The acid is used together with zinc and copper salts to [illegible] the fungistatic effect of the acid and the anti-fungal action of copper salts.

Antifungal antibiotics:

A. Nystatin:

It is derived from *Streptomyces noursi*. It is active against *Candida albicans*. Nystatin has local action; therefore, it is used to control *Candida* infection in the [illegible] and alimentary canal.

It is [illegible] active in the ear and on the skin. The drug can be used for the treatment of mastitic yeast infection at a rate of 100 000 units/quarter.

B. Amphotericin B:

It is derived from *Streptomyces venezullae* and used locally as nystatin.

C. Greseofullvin:

It is produced by the growth of certain stains of *Penicillium griseofulvium*. It is highly effective against *Trichophyton* and *Microsporum species* which causing ringworm in cattle horse and cats. This drug is given orally and absorbed from the GIT into the blood stream. The compound has the affinity to be concentrated in the keratinizing epithelium.

Dose: 1-10 mg/kg b.wt. 10 - 14 days in large animals and for 6-12 weeks, for small animals (15 - 20 mg/kg).

Mode of action

Griseofulvin interfers with the polymerization of the microtubular protein into microtubules. This is a fungistatic effect, and cure depends on the shedding of the infected layers.

Imidazole derivatives:

Thiabendazole: It has anthelmintic and antimycotic activities. It is effective in treating ringworm in cattle.

Miscellaneous antifungals:

Dichlorophen:

It is one of the most available and useful fungicides. It is used in the form of ointment (2 %) as well as in alcoholic solutions. One of its advantages is the low number of dressing required; therefore bovine ringworm has been cleared up following two dressing only.

Monosulfiram:

It has fungicidal activity.

Copper sulphate:

This is widely used by farmers as a home remedy for ringworm in the form of ointment 5 % or as watery solutions of 1-2 %.

Crystal violet:

It is a member of rosaniline dyes and is effective fungistatic aganist *microsporum* and *trichophyton species*.

Iodine preparations: Among iodine preparations are strong Tr. iodine (5 %), weak Tr. iodine (2.5 %) and iodine ointment. Iodine is used for treatment of ringworm and other fungal infections. Injection of sodium iodide solution is the moat useful treatment of the ringworm.

Sulphur:

The inorganic sulphur ointment with or without other compounds as resercinol have been used aganist ringworm in animals and man.

XV.III. ANTIVIRAL DRUGS

These are drugs which used for treatment of viral infections. No products have been registered for veterinary use as antiviral agents. Most of antiviral drugs are toxic to the host cells and unsafe for use. They include:

1- Amantadine:

It is a cyclic amine. It is used against sensitive strains of influenza virus. It is used for treatment of respiratory viral infection in chickens.

2- Idoxuridine:

It has the ability to incorporate DNA and it also inhibits synthesis of DNA. It is effective against herpesvirus and poxvirus.

3- Cytarabine:

In cell culture, it has activity against herpesvirus, poxvirus and rabies. It is used topically, but systemic activity has not been established.

4- Adenine arabinoside:

In experimental animals, it has been found effective topically for herpetic keratitis and systemically for encephalitis caused by herpesvirus. The drug is deaminated and the product has no/low antiviral activity.

5- Methisazone:

It has antiviral activity in cell culture against poxvirus, arboviruses and [illegible].

6- Interferon:

It is a proteinaceous substance released from mammalian cells with the ability to cause other cells to resist a viral infection. It gives protection against a wide variety of RNA viruses and DNA viruses. The antiviral

activity may be attributed to inhibition of RNA - dependent polymerases brought into the cell by a virus or attenuates ribosomes.

7- Polyriboinosinic acid:

It is an important inducer of interferon. It is related to a rapid increase in interferon concentrations and a protective effect aganist local or systemic viral infections where administered topically or systemically respectively.

8- Gamma globulin:

It has been reported to be effective for preventing various viral infections in man (e.g., infectious hepatitis, measles, poliomyelitis, chicken pox).

XV.IV. VACCINES AND ANTISERA

Types of immunity:

Immunity is the resistance of an immune individual to the attack of a pathogenic organism or a toxic product of a pathogenic organism.

The immunity is due to:

1. Specific antibodies.

2. Non-specific factors as properdin and immunoalglutinin.

Immunity may be active or passive:

A) **Passive artificial immunity:**

This type of immunity is created by the parenteral injection of hyperimmune sera which may be used either prophylactically or therapeutically.

A hyperimmune serum is a serum which contains a high concentration of specific antibodies and is obtained by repeatedly injecting the dooner animal with increasing doses of a standard antigen. Blood is then drawn from these animals and subjected to various processes to produce sterile hyperimmune serum (antiserum) .

Antisera:

They are of 3 types;

1- **Antitoxic sera:** In which the immunity of the donor has been developed by the injection of a modified toxin (toxoid) or unmodified toxin. Antisera prepared against toxins or toxoids are known as antitoxins e.g. tetanus and botulinus antitoxin.

2- Antibacterial sera; In which the antigen has been a suspension of bacterial bodies. There are:

a)Agglutinins.

b) Precipitins.

c) Bacteriolysins.

d) Opsnoins (heat stable, induce phagocytois by W.B.Cs).

3- Antiviral sera: which is prepared as other sera but the antigen used is a vaccine prepared from a specific virus.

B) Active artificial immunity:

Active immunity produces stronger and permanent protection.

Created by injections of toxoids, bacterial vaccines or viral voccines.

1. Toxoids:

It is a toxin which has been treated in such a manner that its poisonous properties have been destroyed without materially affecting the ability to stimulate antibody formation.

2. Bacterial vaccines:

It is suspension of killed bacteria or of living attenuated bacteria.

3. Viral vaccines:

The principles that apply to bacterial vaccines also apply to viral vaccines.

Table (20):

Some pharmacokinetic parameters of sulfamethazine (sulfadimidine) in animals

Species	Dose (mg/kg)	Route	V_d (L/kg)	$t_{1/2}$ (hr)	Clearance (mL/hr/kg)
Cattle	107	IV	0.346	NR	NR
Cattle (male)	200	IV	0.37	5.82	45
Cattle (female)	200	IV	0.24	3.64	54
Calves (62-70 days old)	10	IV	NR	5.2	NR
Calves (68-76 days old)	100	IV	NR	5.7	NR
Cows (4-5 yr old)	10	IV	NR	4	NR
Cows (3-5 yr old)	100	IV	NR	5.9	NR
Cows (5-6 yr old)	200	IV	NR	5.5	NR
Pigs (9 wk old)	50	IV	0.51	16	21
Pigs (10 wk old)	20	IV	0.604	10	42
Pigs (10 wk old, given in drench)	20	PO	NR	11.9	NR
Pigs (10-wk old, given in medicated feed)	20	PO	NR	16.6	NR
Pigs (male, 18-32 kg)	20	IV	0.55	12.4	25
Gilts (12-13 wk old)	107.5	IA	0.493	15.61	NR
Barrows (12-13 wk old)	107.5	IA	0.614	17.7	NR
Boars (12-13 wk old)	107.5	IA	0.542	16.63	NR
Pigs (normal castrated males and intact females)	50	IV	0.50	15	23
Pigs (castrated males and intact females infected with *S. suum*)	50	IV	0.52	20	17
Goat	100	IV	0.316	2.77	81
Goats (adult and fed)	100	IV	0.9	4.75	135.6
Goats (adult and fasted)	100	IV	0.897	7.03	69.6
Goats (adult male)	20	IV	0.28	8.7	20
Goats (adult female)	20	IV	0.18	2.13	70
Goats (12 wk old)	100	IV	0.43	1.97	134
Goats (18 wk old)	100	IV	0.507	2.56	106
Sheep	100	IV	0.297	4.72	44.6
Sheep (male)	100	IV	0.4	4.5	90
Ewes	100	IV	0.474	9.51	35.07
Ewes (dosed in summer months)	100	IV	0.37	3.64	63
Ewes (dosed in winter months)	100	IV	0.49	3.92	85
Sheep (ewes and rams)	100	IV	0.41	10.8	41
Sheep (ewes and rams)	100	PO	NR	4.3	NR
Sheep (ewes and rams)	391	PO	NR	14.3	NR
Sheep (ewes and rams)	100	IV	0.37	3.64	NR
Sheep (ewes and rams)	107.5	IV	0.293	5.87	NR
Sheep (ewes and rams)	107.5	IV	0.327	7.09	NR
Ponies (breed unknown)	160	IV	0.63	11.4	42.1
Ponies (Shetland)	20	IV	0.33	5.4	55.2
Mare (2 yr old)	20	IV	0.47	5	65
Mare (2 yr old)	200	IV	0.56	6	67
Mare (22 yr old)	20	IV	0.38	9.5	28
Mare (22 yr old)	200	IV	0.36	14.6	27
Stallion (1.5 yr old)	20	IV	0.44	9.5	32
Stallion (1.5 yr old)	200	IV	0.65	11	41
Dogs (normal)	100	IV	0.628	16.2	22.4
Dogs (febrile)	100	IV	0.495	16.7	20.2
Rabbits (male)	35	IV	0.42	0.4	73.6
Rabbits (female)	35	IV	0.23	0.39	40.8
Carp (10° C)	100	IV	1.15	50.3	16.14
Carp (20° C)	100	IV	0.9	25.6	24.66
Rainbow trout (10° C)	100	IV	1.2	20.6	41.1
Rainbow trout (20° C)	100	IV	0.83	14.7	39.9
Camel	50	IV	0.73	13.2	40
Camel	100	IV	0.394	7.36	40.9
Buffalo (female)	200	IV	1.23	12.36	193.2

Note: NR = not reported; IV = intravenously; IA = intra-arterially; PO = orally.

Table (21)

Some pharmacokinetic parameters of trimethoprim in animals

Species	Dose[a] (mg/kg)	Route	V_d (L/kg)	$t_{1/2}$ (hr)	Clearance (mL/hr/kg)
Cows	8/40	IV	NR	1.18	NR
Pigs	4	IV	1.8	3.3[b]	0.55
Pigs (fed)	8	PO	NR	10.6[b]	NR
Pigs (fasted)	8	PO	NR	6.5[b]	NR
Calves (male, 1 day old)	5/25	IV	1.67	8.4	2.8
Calves (male, 7 days old)	5/25	IV	2.23	2.11	2.0
Calves (male, 42 days old)	5/25	IV	2.36	0.9	28.9
Calves (7 wk old, milk diet)	5/25	SC	NR	3.4	126.0
Calves (13 wk old, milk diet)	5/25	SC	NR	3.4	124.8
Calves (7 wk old, grain diet)	5/25	SC	SC	4.4	105.6
Calves (13 wk old, grain diet)	5/25	SC	NR	3.6	112.2
Calves (7 days old)	5/25	IV	28.72	4.44	102.0
Carp (10° C)	20/100	IV	3.1	40.7	47.0
Carp (20° C)	20/100	IV	4.0	20.0	141.0
Broilers	4/2[c]	PO	NR	0.63	NR
Quail (*Coturnix coturnix japonica;* male and female)	10	PO	NR	2.98	NR
Quail (*Coturnix coturnix japonica;* male and female)	4	IV	2.99	2.38	1.129
Pigs	5/25 (Tribrissen 12%)	PO	NR	3.35	NR
Pigs	5/25 (Trimazin 12%)	PO	NR	4.86	4.86
Pigs	5/25 (Trimazin Forte 24%)	PO	NR	5.92	NR

Note: NR = not reported; IV = intravenously; SC = subcutaneously; PO = orally.

Table (22):

Pharmacokinetic parameters of selected penicillins in domestic species

Drug	Species	V_d* (L/kg)	Clearance (mL/kg/min)	Elimination half-life (hr)
Penicillin G (sodium or potassium)	Dogs	0.16	3.6	0.50
	Horses	0.65	8.5	0.88
	Cattle			0.50
Procaine penicillin G	Dogs	0.16	3.6	0.50
	Horses	0.65	3.6	0.88
	Sheep			1.42
Benzathine penicillin	Horses	0.65		0.88
	Sheep	0.23	12.4	
	Camels	0.15	4.9	
Ampicillin	Dogs	0.20	1.9	1.25
	Horses	0.18		0.62
	Cattle			1.20
	Sheep	6.39	50.0	1.58
	Goats	7.15	57.0	1.58
Amoxicillin	Dogs	0.20	1.9	1.25
	Foals	0.27	5.7	0.74
	Horses	0.33	5.7	0.66
	Sheep	0.22	10.1	0.77
	Goats	0.47	11.4	1.12
Oxacillin	Dogs	0.30	6.9	0.50
	Horses	0.60	11.6	0.60
Cloxacillin	Dogs	0.20	4.6	0.50
Dicloxacillin	Dogs	0.20	3.5	0.67
Methicillin	Cattle			0.30
Carbenicillin	Dogs	0.19	1.8	1.25
	Horses	0.40	4.6	1.00
Ticarcillin	Dogs	0.34	4.3	0.95
	Horses			0.90

*V_d = volume of distribution.

Table (23)

Recommended dosages for penicillins

Drug	Species	Dose	Route	Interval (hr)
Penicillin G (sodium or potassium)	Horses	20,000–60,000 IU/kg	IM, IV	6–8
	Dogs and cats	22,000–55,000 IU/kg	IM, IV, SQ	6–8
Procaine penicillin G	Horses	20,000–100,000 IU/kg	IM	12
	Cattle	10,000–66,000 IU/kg	IM, SQ	12–24
	Swine	40,000 IU/kg	IM	24
	Dogs and cats	20,000 IU/kg	IM, SQ	12–24
Benzathine penicillin	Horses	50.000 IU/kg	IM	48
	Cattle	10,000–66,000 IU/kg	IM, SQ	48
	Dogs and cats	40.000–50,000 IU/kg	IM	120
Penicillin V (potassium)	Horses	66,000–110,000 IU/kg	PO	6–8
	Dogs and cats	5.5–11 mg/kg	PO	6–8
Ampicillin	Horses	10–22 mg/kg	IV, IM	8
	Cattle	11–22 mg/kg	SQ, IM	12
		4–10 mg/kg	PO	12–24
	Dogs and cats	10–20 mg/kg	IV, SQ	6–8
		22–33 mg/kg	PO	8
	Swine	6–8 mg/kg	SQ, IM	8
Amoxicillin	Horses	20–30 mg/kg	IM, PO	6–2
	Cattle	6–11 mg/kg	IM, SC	12–24
	Dogs and cats	10–22 mg/kg	PO	8
		5–11 mg/kg	IM, IV, SQ	8
Amoxicillin + Cavulanate	Dog	12.5–25 mg/kg	PO	8–12
	Cat	62.5 mg/kg	PO	8–12
Cloxacillin	Dogs and cats	20–40 mg/kg	IM, IV, PO	8
Dicloxacillin	Dogs and cats	10–50 mg/kg	PO	8
Oxacillin	Horses	20–50 mg/kg	IM, IV	6–8
	Dogs and cats	20–40 mg/kg	PO	8
		5.5–11 mg/kg	IV, IM	4–8
Carbenicillin	Dogs and cats	55–100 mg/kg	IV, PO	8
Ticarcillin	Dogs and cats	40–110 mg/kg	IV, IM, SC	6

Tables (24, 25)

Pharmacokinetic parameters of selected cephalosporins in domestic species

Drug	Species	V_d[a] (L/kg)	Clearance (mL/kg/min)	Elimination half-life (hr)
Cephapirin	Foals[b]	1.06	18.4	0.70
	Horses	0.17	10.0	
	Cows[c]		12.7	
	Dogs	0.32	8.9	0.42
Cephalothin	Horses	0.15	13.6	0.25
Cefadroxil	Horses	0.46	7.0	0.77
Cefazolin	Foals	0.45	0.4	1.37
	Horses	0.19	5.5	0.67
	Calves	0.17	5.8	0.62
	Dogs	0.70	10.4	0.80
Cephalexin	Calves	0.32	1.9	2.00
	Cows	0.39	10.5	0.58
	Sheep	0.17	5.0	1.20
Cefoxitin	Calves			1.12
	Horses	0.12	4.3	0.82
Cepfaronide	Sheep	0.39	2.7	
Ceftriaxone	Dogs			0.85
	Sheep	0.30	3.7	
	Calves			1.40
Ceftazidime	Dogs			0.82
	Sheep	0.36		1.60
Cefoperazone	Calves			0.89
	Sheep	0.16	2.7	
Moxalactam	Calves			2.40

[a] V_d = volume of distribution.
[b] Neonatal.
[c] Lactating.

Recommended dosages for cephalosporins

Drug	Species	Dose (mg/kg)	Route	Interval (hr)
Cefadroxil	Dogs/Cats	22	PO	8–12
	Horses	25	PO	4
Cephalexin	Horses	22–33	PO	6
	Dogs/Cats	22	PO	8
Cephapirin	Horses	20–30	IM, IV	8–12
	Dogs/Cats	10–30	IV, IM, SC	6–8
Cephalothin	Horses	11–20	IV, IM	6
	Cattle	55	SC	6
	Dogs/Cats	10–30	IM, IV, SC	6–8
Cefazolin	Horse	15–20	IV, IM	8
	Dogs/Cats	20–35	IM, IV, SC	6–8
Cefoxitin	Dogs/Cats	30	IV	8
	Foals	20	IV	4–6
Cefotetan	Dogs/Cats	30	IV	8
Cefotaxime	Dogs/Cats	25–50	IV, IM, SC	8
	Foals	20–30	IV	6
	Goats	50	IV	12
Ceftiofur	Cattle	1	IM	24

Table (26, 27)

Some pharmacokinetic parameters of chlortetracycline in some food-animal species

Species	Dose (mg/kg)	Route	V_d (L/kg)	$t_{1/2}$ (hr)	Clearance (mL/min/kg)
Turkey	0.9	IV	0.2284	0.877	3.77
Pigs	11.0	IV	1.3883	NR	0.3071
Calves (milk fed)	11.0	IV	3.34	8.89	260.52 L/hr/kg
Calves (conventionally fed)	11.0	IV	1.93	8.25	162.12 L/hr/kg

Note: NR = information not reported; IV = intravenous.

Some pharmacokinetic parameters of tetracycline recently reported in some species

Species	Dose (mg/kg)	Route	V_d (L/kg)	$t_{1/2}$ (hr)	Clearance (mL/min/kg)
Gilts	11	IA	1.06	NR	0.4
Chickens	65	IV	0.174	2.772	1.632
Rabbits (male and female)	10	IV	1.047	2	6.1
Channel catfish (*Ictalurus punctatus*) (27° C)	4	IV	0.513	16.5	0.365

Note: NR = information not reported; IV = intravenous; IA = intra-arterial.

Table (28)

Some pharmacokinetic parameters of oxytetracycline in some species

Species	Dose (mg/kg)	Route	V_d (L/kg)	$t_{1/2}$ (hr)	Clearance (mL/min/kg)
Horses	10	IV	0.6728	12.953	0.6583
Ponies	10	IV	1.0482	14.949	1.013
Donkeys	10	IV	0.7765	6.464	1.523
Horses (adult)	2.5	IV	1.35	10.5	NR
Pigs	10	IV	1.49	5.99	2.88
Pigs (normal)	50	PO	1.44	5.92	
Pigs (pneumonia)	50	PO	1.9	14.1	
Pigs	20	IV	5.18	3.68	4.15
Cows (adult)	2.5	IV	1.04	9.12	NR
Dairy cows	5	IV	0.917	2.63	1.24
Dairy cows[a]	5.23	IV	1.01	2.58	1.45
Veal calves	40	IV	18.144	7.34	2.246
Veal calves	20	IV	18.541		2.167
Calves (3 wk old)	7.54	IV	2.48	13.5	
Calves (12 wk old)	6.88	IV	1.52	8.8	
Calves (14 wk old)	17	IV	1.83	10.8	
Buffalo calves (female)	22	IV	0.32	3.6	1.02
Dogs	5	IV	2.096	6.02	4.23
Rabbits	10	IV	0.668	1.32	14.6
Turkeys	1	IV	3.622	0.7298	3.6579
Rainbow trout	5	IV	2.988	81.5	0.423
African catfish	60	IV	1.33	80.3	0.19
Red-necked wallaby	40	IV	2.041	11.4	NR

Note: NR = information not reported; IV = intravenous; PO = per os. All formulations were reported to be or are assumed to be HCl unless otherwise noted.
[a]Oxytetracycline dihydrate formulation tested.

Table (29)

Some pharamcokinetic parameters of doxycycline in some species

Species	Dose (mg/kg)	Route	V_d (L/kg)	$t_{1/2}$ (hr)	Clearance (mL/min/kg)
Pigs (9 wk old)	20	IV	0.53	4.04	1.67
Calves	5	IV	NR	9.5	1.2 (mg/L)
Calves (functional rumen)	20	IV	1.31	14.9	1.07
Calves (nonfunctional rumen)	20	IV	1.81	9.9	2.2
Cats	5	IV	0.34	4.56	1.09
Dogs	5	IV	0.93	6.99	1.72
Dogs	5	IV	1.468	10.36	1.68
Goats (lactating)	5	IV	9.78	16.63	6.91

Note: IV = intravenous; NR = information not reported.

Table (30)

Some pharmacokinetic parameters of minocycline HCl in some species

Species	Dose (mg/kg)	Route	V_d (L/kg)	$t_{1/2}$ (hr)	Clearance (mL/min/kg)
Dogs (2-compartment model)	5	IV	1.952	6.93	3.347
Dogs (3-compartment model)	5	IV	2.001	7.24	3.424
Sheep (normal)	2.2	IV	1.32	2.58	5.94
Sheep (hypoproteinemic)	2.2	IV	1.67	2.91	5.60

Note: IV = intravenous.

Table (31)

Single-dose intravenous serum or plasma pharmacokinetics of gentamicin in various species

Species	Dose (mg/kg)	$V_{d(area)}$ (L/kg)	$V_{d(ss)}$ (L/kg)	Cl_B (mL/min/kg)	$t_{1/2(\beta)}$ (hr)	$t_{1/2(\gamma)}$ (hr)
Dogs (juvenile)	10	0.354 (0.036)	ND	4.08 (0.62)	1.01 (0.12)	N/A
Dogs	10	0.38 (0.029)	ND	4.20 (0.70)	1.05 (0.13)	N/A
Dogs	10	0.30 (0.06)	ND	3.44 (0.38)	1.01 (0.08)	N/A
Dogs	10	0.335 (0.094)	ND	2.94 (0.67)	1.36 (0.09)	N/A
Dogs	4.4	0.227 (0.076)	0.175 (0.033)	2.27 (0.41)	1.09[a]	N/A
Dogs	4.4	NR	8.56 (4.48)	1.45 (0.11)	1.04[a]	154.3[a]
Dogs	4	0.255	ND	3.33	1.06	N/A
Dogs	3	NR	0.172 (0.025)	2.29 (0.48)	0.91 (0.25)	N/A
Cats	4.4	0.190	0.180	1.61	1.36	N/A
Cats	5	ND	0.14 (0.20)	1.38 (0.35)	1.25 (0.30)	86[a]
Cows	5	0.19 (0.04)	0.16 (0.032)	1.32 (0.17)	1.83 (0.18)	N/A
Cattle (1 day old)	4.4	0.393 (0.040)	0.376 (0.041)	1.92 (0.43)	2.49 (0.73)	N/A
Cattle (5 days old)	4.4	0.413 (0.050)	0.385 (0.044)	2.44 (0.34)	1.99 (0.33)	N/A
Cattle (10 days old)	4.4	0.341 (0.021)	0.323 (0.020)	2.02 (0.27)	1.97 (0.21)	N/A
Cattle (15 days old)	4.4	0.334 (0.039)	0.311 (0.029)	2.10 (0.32)	1.85 (0.13)	N/A
Cattle (4-5 weeks old)	3	1.95 (1.24)	0.75 (0.20)	4.9 (1.9)	3.96 (1.67)	N/A
Cattle (adult)	4.4	0.140 (0.020)	0.140 (0.020)	1.29 (0.26)	1.26 (0.19)	N/A
Horses	5	0.254 (0.031)	0.24 (0.03)	2.54 (0.33)	2.54 (0.33)	N/A
Horses (2-3 months old)	4.5	ND	0.306 (0.094)	1.65 (0.79)	3.23 (0.62)	N/A
Horses	2.2	ND	0.15 (0.001)	0.87 (0.05)	3.85 (0.40)	N/A
Horses	2.2	ND	1.74 (0.59)	0.68 (0.17)	3.51 (0.59)	142 (31)
Horses	3	0.202 (0.028)	0.173 (0.012)	1.41 (0.19)	1.66 (0.06)	N/A
Ponies	5	0.20 (0.01)	0.19 (0.01)	1.27 (0.18)	1.82 (0.22)	N/A
Mammoth asses[d]	2.2	0.12 (0.025)	ND	1.22 (0.18)	2.07	ND
Mammoth asses[e]	2.2	0.088 (0.028)	ND	1.29 (0.07)	0.84	5.12
Sheep	2.2	0.194 (0.059)	ND	1.56 (0.40)	1.44 (0.085)	N/A
Sheep	3	ND	0.408 (0.196)	0.660 (0.256)	1.33[a]	41.9 (18.5)
Sheep	10	ND	0.243 (0.026)	1.03 (0.015)	2.4 (0.5)	30.4 (18.9)
Sheep	10	ND	0.384 (0.195)	0.805 (0.317)	1.72[a]	88.9 (19.8)
Sheep	20	ND	0.709 (0.751)	0.882 (0.342)	1.77[a]	167.2 (42.7)
Sheep (Desert)	3	0.27	ND	0.07	4.20	ND
Goat	3	0.22	ND	0.08	1.041	ND
Pigs	2	0.32 (0.032)	0.24 (0.03)	1.66 (0.12)	1.9 (1.47–4.89)	20.2 (13.9–34.6)
Pigs (newborn)	5	ND	0.80	ND	5.19	ND
Pigs (42 days)	5	ND	0.50	ND	3.50	ND
Rabbits	20	ND	0.52–0.95[b]	2.90–4.0	0.98–1.15	11.4–15.1
Rabbits	3.5	ND	0.114 (0.020)	2.82 (0.97)	0.74	ND

Table (31 continued)

Single-dose intravenous serum or plasma pharmacokinetics of gentamicin in various species (*continued*)

Species	Dose (mg/kg)	$V_{d(area)}$ (L/kg)	$V_{d(ss)}$ (L/kg)	Cl_B (mL/min/kg)	$t_{1/2(\beta)}$ (hr)	$t_{1/2(\gamma)}$ (hr)
Hawks[c]	10	0.24 (0.03)	N/A	2.09 (0.16)	1.35 (0.18)	N/A
Owls[c]	10	0.23 (0.02)	N/A	1.41 (0.10)	1.93 (0.24)	N/A
Eagles[c]	10	0.21 (0.01)	N/A	1.01 (0.06)	2.46 (0.32)	N/A
Catfish	1	0.156	NR	0.126	12.2	N/A
Catfish	10	0.176	ND	0.215	11.87	N/A
Guinea pigs	40	ND	ND	3.4	1.01	1.01
Buffalo calves	5	0.43	ND	54.61	5.69	ND
Turkeys	5	0.190	0.172	49.8	2.570	ND
Roosters	5	0.228 (0.019)	0.209 (0.013)	0.775 (0.132)	3.38 (0.62)	N/A

Source: Adapted from Brown and Riviere 1991.
N.B Values reported as arithmetic mean followed by SD or SEM in parentheses. N/A = not applicable (inappropriate term for the model used); ND = not determined; NR = not reported.

[a]Harmonic mean: data are IV and IM data pooled together.
[b]Range.
[c]One-compartment model used.
[d]Best described using a two-compartment open model
[e]Best described using a three-compartment open model.

Tables (32, 33)

Single-dose intravenous pharmacokinetics of amikacin in various species

Species	Dose (mg/kg)	$V_{d(area)}$ (L/kg)	$V_{d(ss)}$ (L/kg)	Cl_B (mL/min/kg)	$t_{1/2\beta}$ (hr)
Cats	5	0.134 (0.008)	NR	110 (15)	NR
Cats	10	0.14 (0.008)	NR	121 (22)	NR
Cats	20	0.18 (0.022)	NR	138 (2.6)	NR
Cats	5	NR	0.17 (0.02)	1.46 (0.26)	79[b] (19)
Horses	4.4	0.20 (0.05)	NR	89.3 (23.4)	1.44[b]
Horses	6.6	0.17 (0.03)	NR	76.6 (11.3)	1.57[b]
Horses	11	0.14 (0.02)	NR	84.7 (13.4)	1.14
Horses	6	0.214	0.207	0.75	2.8
Ponies	6	0.191	0.162	1.37	1.6
Donkeys	6	0.156	0.150	0.97	1.9
Dogs[a]	5	0.26 (0.23–0.29)	NR	2.82 (2.29–3.22)	1.07 (0.95–1.22)
Dogs[a]	10	0.239 (0.18–0.27)	NR	2.66 (2.32–2.89)	0.98 (0.90–1.07)
Dogs[a]	20	0.36 (0.32–0.38)	NR	3.57 (3.31–4.73)	1.03 (0.90–1.33)
Calves	7.5	350	NR	1.5	150.5
Sheep	7.5	200	NR	0.7	115.5
African grey parrots	5	289	233	188	1.06
African grey parrots	10	184	122	142	0.90
African grey parrots	20	444	308	229	1.34
Dogs	25	0.25	NR	34	0.85
Humans	125	16.26 (1.7)	NR	81 (6)	2.8 (0.26)

Source: Adapted from Brown and Riviere 1991.
Note: NR = not reported.
[a] Median (range); total dose (mg); mL/min.
[b] Harmonic mean (±SD).

Nonintravenous disposition values for amikacin in various species (means vith standard deviations in parentheses)

Species	Dose (mg/kg)	Route	V_d/F (L/kg)	Cl_B/F (mL/min/kg)	$t_{1/2}$ (hr)	F (%)
Horses	4.4	IM	NR	NR	NR	100
Horses	6.6	IM	NR	NR	NR	100
Horses	11	IM	NR	NR	NR	100
Cats	5	IM	0.16 (0.004)	132[a] (13)	NR	NR
Cats	10	IM	0.2 (0.02)	150[a] (10)	NR	NR
Cats	20	IM	0.19 (0.02)	121[a] (21)	NR	NR
Cats	5	SC	0.19 (0.01)	138[a] (13)	NR	NR
Cats	10	SC	0.21 (0.01)	117[a] (6)	NR	NR
Cats	20	SC	0.19 (0.01)	141[a] (21)	NR	NR
Cats	5	IM	ND	ND	119	90 (36)
Cats	5	SC	ND	ND	118	100 (19)
Sheep	7.5	IM	ND	ND	1.96	87
Calves	7.5	IM	ND	ND	1.94	99
African grey parrot	5	IM	ND	ND	1.08	98
African grey parrot	10	IM	ND	ND	1.04	61
African grey parrot	15	IM	ND	ND	0.97	106
Gopher snake (25° C)	5	IM	0.29 (0.04)	2.8 (0.29)	1.2 (0.17)	ND
Gopher snake (37° C)	5	IM	0.63 (0.31)	5.83 (1.6)	1.25 (0.5)	ND

Source: Adapted from Brown and Riviere 1991.
ND = not determined; NR = not reported.
[a] mL/min

Table (34)

Selected serum pharmacokinetic parameters of chloramphenicol in animals

Species	Dose (mg/kg)	Route	Formulation	Half-life ($t_{1/2\beta}$) (hr)	(l/kg) V_d	Comments
Dogs	22	IV	Base	4.2	1.77	Dissolved in 50% aqueous solution of N,N,di-methyl-acetamide
Felines	22	IV	Base	5.1	2.36	Dissolved in 50% aqueous solution of N,N,di-methyl-acetamide
Sheep	30	IV	Base	1.702	0.691	
	30	SC	Base	17.93	NA	
	30	IM	Base	2.71	NA	
Adult swine	22	IV	Base	1.3	1.05	Dissolved in 50% aqueous solution of N,N,di-methyl-acetamide
Piglets	25	IV	Base	12.7	0.9411	Normal piglets
	25	IV	Base	17.2	0.9549	Colostrum-deprived piglets
Goats	25	IV	Succinate	1.22	1.683	Nonfebrile animals
	25	IV	Succinate	1.29	1.962	Febrile animals
	25	IM	Succinate	1.46	3.019	Nonfebrile animals
	25	IM	Succinate	1.45	2.769	Febrile animals
Goats	22	IV	Base	2.0	1.33	Dissolved in 50% aqueous solution of N,N,di-methyl-acetamide
Goats	10	IV	Succinate	1.47	0.312	Normal animals
	10	IV	Succinate	3.97	0.287	Starved animals
Goats	22	IV	Base	2.0	1.33	Dissolved in 50% aqueous solution of N,N,di-methyl-acetamide
Goats	10	IV	Succinate	1.47	0.312	Normal animals
	10	IV	Succinate	3.97	0.287	Starved animals
Cattle	40	IV	Base	2.81	0.351	
	90	IM	Base	1.345	NA	2 doses 48 hr apart
	90	SC	Base	1.153	NA	2 doses 48 hr apart
Calves	30	IV	Base	3.98	1.208	Age not reported; average weight = 73 kg
Calves						
(1 day old)	25	IV	Base in PG vehicle	7.56	1.031	
(7 days old)	25	IV	Base in PG vehicle	5.96	0.808	
(14 days old)	25	IV	Base in PG vehicle	4.0	0.903	
(28 days old)	25	IV	Base in PG vehicle	3.69	0.69	
(9 months old)	25	IV	Base in PG vehicle	2.47	1.38	
Horses	22	IV	Base in PG vehicle	0.51–0.78	0.86–1.26	
Ponies	22	IV	Base	0.9	1.02	Dissolved in 50% aqueous solution of N,N,di-methyl-acetamide

Table (34 continued)

Continued

Species	Dose (mg/kg)	Route	Formulation	Half-life ($t_{1/2\beta}$) (hr)	V_d (l/kg)	Comments
Foals						
(1 day old)	25	IV	Succinate	5.29	1.1	
(3 days old)	25	IV	Succinate	1.35	0.759	
(7 days old)	25	IV	Succinate	0.61	0.491	
(14 days old)	25	IV	Succinate	0.51	0.426	
(42 days old)	25	IV	Succinate	0.34	0.362	
(1-9 days old)	50	IV	Succinate	0.95	1.6	After oral suspension administered oral, availability was 83% and half-life of 2.54 hr
Rabbits	100	IV	Succinate	1.1575	NA	
Chickens	20	IV	Succinate	8.32	0.24	Normal animals
	20	IV	Succinate	26.21	0.3	*E. coli*-infected animals
	20	IM	Succinate	7.84	0.44	
	20	PO	Succinate	8.26	0.41	

Note: NA = data not available; PG = propylene glycol.

Tables (35, 36 & 37)

Selected pharmacokinetic parameters of florfenicol in animals

Species	Dose mg/kg	Half-life (hr)	Absorption (%)	V_d (L/kg)	C_{MAX} (mcg/mL)
Cats	22 (all routes)	4 (IV) 7.8 (oral) 5.6 (IM)	> 100 (oral) > 100 (IM)	0.61	57 (IV) 28 (oral) 20 (IM)
Dogs	20 mg/kg (all routes)	2 (IV) 18 (SC) 9 (IM) 3 (oral)	28 (SC) 16 (IM) > 100 (oral)	1.2	44 (IV) 0.93 (SC) 1.64 (IM) 17 (oral)
Sea turtles	20 (IM, IV)	2–7.8 hr (IM)	67 (IM)	10-60 L/kg	0.5-0.8 (IM)
Horses	22 (IV)	1.83	81 (IM) 83 (oral)	0.72	4 (IM) 13 (oral)
Cattle	50 (IV)	3.2	ND	0.67	157.7
Feeder calves	20 (IV)	2.65	ND	0.88	73
Feeder Calves	20 (IM)	18.3	78.5	ND	3.07
Veal calves	22 (oral)	ND	88	ND	11.3
Veal calves	22 (IV)	2.87	ND	0.78	66
Veal calves	11 (IV)	3.71	ND	0.91	26.35
Veal calves	11 (oral)	3.7	89	ND	5.7

Note: Route of administration used is listed in parentheses. V_d is volume of distribution, C_{MAX} is the maximal concentration after administration with route listed in parentheses. ND = not determined.

Selected serum pharmacokinetic parameters of erythromycin in animals

Species	Dose (mg/kg)	Route	Formulation	Half-life ($t_{1/2\beta}$) (hr)	V_d (L/kg)
Cows	12.5	IV	Base	3.16	0.789
Calves	15	IV	Base in PG vehicle	2.91	0.835
	15	IM	Base in PG vehicle	5.81	NA
	15	SC	Base in PG vehicle	26.87	NA
Calves	30	IV	Base in PG vehicle	4.09	1.596
	30	IM	Base in PG vehicle	11.85	NA
	30	SC	Base in PG vehicle	18.3	NA
Mice	10	IV	Base	0.65	3.6
Rats	25	IV	Base	1.27	9.3
Rabbits	10	IV	Base	1.4	6.8
Dogs	10	IV	Base	1.72	2.7

Note: NA = data not available.

Selected serum pharmacokinetic parameters of tylosin in animals

Species	Dose (mg/kg)	Route	Half-life ($t_{1/2\beta}$) (hr)	V_d (L/kg)
Dogs (Beagle)	10	IV	0.9	1.7
Ewes	20	IV	2.05	NA
Goats	15	IV	3.04	1.7
Cows	12.5	IV	1.62	1.1
Cows	20	IV	2.14	NA
Calves				
(2 days old)	10	IV	2.32	7
(1 wk old)	10	IV	1.26	7.2
(2 wk old)	10	IV	0.95	11.1
(4 wk old)	10	IV	1.53	9
(>6 wk old)	10	IV	1.07	11.1
Avians (emus)	15	IV	4.7	NA
Avians (quail, pigeons, cranes)	15	IM	1.2	NA

Note: NA = data not available.

Table (38)

Pharmacokinetic comparison of fluoroquinolones

Drug	Dose studied (mg/kg)	Recommended daily dose (mg/kg)	$t_{1/2}$[a] (hr)	Vd (area)[b] (L/kg)	C_{max} (µg/mL)	AUC[c] (µg·hr/mL)	%F	Assay[h]
Dogs								
Enrofloxacin	5.0 IV	5.0	2.7–3	5.0–5.6	—	4.05–4.34	—	HPLC
Enrofloxacin	5.0	5.0	2.52	2.5	1.12 (oral)	7.27	72.3	HPLC
Enrofloxacin	5.8	5.0	4.4 (IV) 2.7 (oral)	4.5	1.44 (oral)	8.2	83.0	HPLC
Enrofloxacin	5.5	2.75–11.0	4.0 (oral)	nd	2.45 (oral)	16.32	nd	Bioassay
Enrofloxacin	5.0	5.0	2.4	4.5	1.16 (oral)	3.9	100	HPLC
Enrofloxacin	5.0	5.0–20.0[c]	4.8	4.2	1.6	8.15	—	HPLC
Ciprofloxacin	5.0	nd	3.17	2.23	0.35	4.18	43.0	HPLC
Ciprofloxacin	5.8[f]	nd	5.2	nd	0.34	7.2	nd	HPLC
Ciprofloxacin	10.0	10.0–20.0	2.4	3.0	—	12.93	—	HPLC
Ciprofloxacin	10.0	10.0–20.0	7.5	—	1.18 (oral)[d]	9.58 (oral)[d]	46[e]	Bioassay
Difloxacin	5.0	5.0–10.0[c]	9.3	4.63	1.8 (oral)	12.93	96.0	nd
Orbifloxacin	2.5	2.5–7.5[c]	5.6	1.5	2.33 (oral)	14.3	97–100	HPLC
Marbofloxacin	2.0	2.0	12.4–14.0	1.9–2.25	1.38 (oral) 1.52 (SC)	18.6–20.95 99 (SC)	100 (oral)	HPLC
Marbofloxacin	2.0	2.0	9.8	1.4	1.35 (oral)	23.31	99.8	HPLC
Marbofloxacin	5.55 and 2.8 mg/kg	2.75–5.55[c]	9.5 (IV) 11 (oral)	1.27	2.0 at 2.8 mg/kg oral; 4.2 at 5.55 mg/kg oral	59.0	94.0	HPLC
Cats								
Enrofloxacin	4.7	5[c]	6.7	6.3	1.66 (oral)	7.2	100	HPLC
Orbifloxacin	2.5	2.5–7.5[c]	5.5	1.4	2.06	10.82	100	HPLC
Horses								
Ciprofloxacin	3.0	Not recommended	4.9 (IV) 10.7 (IM)	0.147	0.77 (IM)	6.97	96.0 (IM)	HPLC
Ciprofloxacin	5.0	Not recommended	2.6 (IV)	3.88	na	4.83	6.8	Bioassay
Enrofloxacin	2.5 and 5.0	5.0 (IV, IM) 5.0–7.5 (oral)	5.9–6.1	0.78 (5 mg/kg)	5.44	58.3	62.5	Bioassay
Orbifloxacin	2.5	2.5–5.0 (oral)	5.1	2.4	1.25 (oral)	9.06	68.3 (oral)	HPLC
Enrofloxacin	5.0 (IV, IM)	5.0 (IV or IM)	4.4 (IV) 9.9 (IM)	2.4	1.28 (IM)	13.2	>100% (IM)	HPLC
Enrofloxacin (foals)	5.0	2.5–5.0	16.5	2.31	2.12 (10 mg/kg oral)	48.54	42.0	HPLC
Mice								
Enrofloxacin	10.0	nd	1.48	10.5	nd	2.45	nd	HPLC
Rats								
Enrofloxacin	7.5	nd	1.8	4.78	nd	5.65	nc	HPLC

Table (38 continued)

Rabbits								
Enrofloxacin	7.5	nd	2.2	4.94	nd	5.52	nd	HPLC
Enrofloxacin	7.5 (IV)	nd	1.87	3.97	na	5.38	na	HPLC
Enrofloxacin	5.0 (IV)	5.0	2.18 (IV)	4.4	na	3.89	na	HPLC
Enrofloxacin	5.0 (IM)	5.0	1.8	na	3.04	3.84	92.0	HPLC
Enrofloxacin	5.0 (IV)	5.0	2.5	2.12	na	8.6	na	HPLC
Enrofloxacin	5.0 (oral)	5.0	2.4	na	0.45	5.4	61.0	HPLC
Cattle								
Enrofloxacin (1-day-old calves)	2.5	2.5–5 per day or 7.5–12.5 SC once	6.61	1.70	nd	13.94	nd	HPLC
Enrofloxacin (1-week-old calves)	2.5	2.5–5 per day or 7.5–12.5 SC once	4.87	2.61	nd	6.73	nd	HPLC
Enrofloxacin (lactating cows)	5.0	nd	1.68 (IV) 5.9 (IM) 5.55 (SC)	1.63	0.73 (IM) 0.98 (SC)	7.42	82.0 (IM) 137.0 (SC)	HPLC
Enrofloxacin (cows)	2.5	nd	2.82	2.98	nd	5.28	nd	HPLC
Enrofloxacin (adult cattle)	5.0	2.5–5 per day or 7.5–12.5 SC once[c]	2.3	1.65	0.73 (SC)	10.08	88.0 (SC)	HPLC
Enrofloxacin (calves)	5.0	2.5–5 per day or 7.5–12.5 SC once[c]	2.2	1.98	0.87 (SC)	7.99	97.0 (SC)	HPLC
Ciprofloxacin (calves)	2.8	nd	2.4	2.5	0.27	nd	53.0 (oral)	HPLC
Sheep								
Enrofloxacin	2.5	5.0 mg/kg/day SC	3.73	2.18	0.78 (IM)	5.47	85.0 (IM)	HPLC
Enrofloxacin	2.5	5.0 mg/kg/day SC	3.8	1.3	0.6 (oral)	10.4	60.6 (oral)	Boassay
Enrofloxacin	2.5	nd	2.5	1.53	nd	8.98	nd	HPLC
Chickens								
Ciprofloxacin	5.0	5.0–15.0 IM, SC, oral	9.01	2.02	4.67	78.04	70.0	Bioassay
Enrofloxacin	10.0	10.0	5.6 (IV)	5.0	1.88 (oral)	16.17	89.2	HPLC
Enrofloxacin	10.0	10.0	10.3 (IV)	4.3	2.44 (oral)	34.51	64.0	HPLC
Ciprofloxacin	5.0	5.0	9.0	2.0	4.67	78.04	70.0 (oral)	Bioassay
Camels								
Enrofloxacin	2.5	2.5 IM, SC	3.58	1.4	1.44 (IM)	18.95	85.0 (IM)	Bioassay
Pigs								
Enrofloxacin	2.5		345	3.34	1.17	5.97	150	HPLC
Enrofloxacin	2.5		7.73	3.5	0.61 (IM)	9.94	95.0 (IM)	HPLC
Enrofloxacin	2.5		5.5	3.95	0.75 (IM)	5.03	101 (IM)	Bioassay
Enrofloxacin	10.0 oral		nd	nd	nd	27.0	73.0–80.0	HPLC
Ciprofloxacin	3.06	nd	2.57	3.83	0.17	2.88	37.0	HPLC

(continued)

Table (38 continued)

Continued

Drug	Dose studied (mg/kg)	Recommended daily dose (mg/kg)	$t_{1/2}$[a] (hr)	Vd (area)[a] (L/kg)	C_{max} (µg/mL)	AUC[a] (µg·hr/mL)	%F	Assay[b]
Dolphins								
Enrofloxacin	5.0	5.0 q24h oral	6.4	nd	1.4	15.4	nd	Bioassay
Fish								
Enrofloxacin trout	5.0 and 10.0	5.0 mg/kg q24h	24.0 and 30.0	3.22 and 2.56	0.945 and 1.28 (15E)	109.2 and 171.3	(oral at 15°) 42 and 49	Bioassay
Enrofloxacin (red pacu)	5.0	5.0 mg/kg q48h IM	29.0	nd	1.64 (IM) 0.8 (oral)	46.3 (IM)	57.0 (relative)	HPLC
Enrofloxacin (Atlantic salmon)	10.0	5.0 mg/kg q24h oral	131.0	22.4	0.29 (oral) 0.54 (oral)	84.3 1.3 (IP)	89.0 (IP) 46 (oral)	Bioassay 66 (IM)

Na = Data not available or not applicable.
Nd = Not determined.
$t_{1/2}$ = Half-life of the terminal portion of the plasma concentration vs. time curve.
Vd = Apparent volume of distribution (area method).
AUC = Area under the curve of the plasma concentration vs. time curve.
C_{max} = Maximum plasma concentration after administration of oral or IM dose.
%F = Percentage of oral or IM administered dose absorbed (determined from comparison of IV dose).
[a]Half-life, Vd, and AUC are from an IV dose unless otherwise noted.
[b]Assay type = Assay using HPLC is able to distinguish between enrofloxacin and ciprofloxacin, and values shown in table represent enrofloxacin. Assays performed by bioassay represent the parent drug and active metabolites. Bioassay may include concentrations of ciprofloxacin.
[c]Registered dose with the FDA in the United States. In some European countries doses may vary or may not include the flexible range. In most cases, when treating non-*Pseudomonas* infections, the lowest dose in the range listed is used.
[d]After multiple dosing with ciprofloxacin, the C_{max} was 1.18 mg/mL and the 12 hr AUC was 9.58 mg/hr/mL.
[e]Oral absorption of ciprofloxacin estimated from a comparison of independent oral and IV studies.
[f]These parameters determined after administration of 5.8 mg/kg of enrofloxacin.

Table (39)

Suggested antifungal drugs and dosages for treating systemic fungal infections in the dog and cat

Disease	Treatment	Daily dose (mg/kg)		Frequency	Comment
		Dog	Cat		
Blastomycosis[a]	Am B initially	0.5	0.25	3 times/week	For life- threatening disease
	then KTZ	10–15	10	12–24 hr	
	ITZ[b]	5	5	12 hr	For non-life-threatening disease
Histoplasmosis[c]	KTZ	10–15	50	12–24 hr	
	Concurrent Am B	0.25–0.5	0.25–0.5	48 hr	Drugs started together; KTZ given alone after condition improves
	and KTZ	10–15	50	12–24 hr	
Cryptococcosis	Am B	0.25–0.5	0.1–0.5	3 times/week	For CNS infections initially
	5–FC	30	30	6 hr	For CNS infections initially
		50	50	8 hr	
		75	75	12 hr	
	FLZ[d]	10–20	10–20	12–24 hr	For CNS infections initially
	KTZ	5–30	5–20	12–24 hr	For maintenance
	FLZ	5–10	5–10	12 hr	For maintenance
Coccidioidomycosis	KTZ	5–10	50	8–24 hr	Not useful in meningitis
	Am B	0.4–0.5		48–72 hr	If CNS is involved
	FLZ	5–10	5–10	12 hr	
	ITZ	5	5	12 hr	
Aspergillosis[e]	FLZ	5–10	5–10	12 hr	For systemic disease
	Enilconazole	10		12 hr	Topical-direct infusion at infection site
Candidiasis	KTZ	5–11	50–100	12–24 hr	For systemic disease
	ITZ	5–7	5–7	12 hr	For systemic disease
	Nystatin				For local mucocutaneous disease
	Miconazole				Applied topically
	Clotimazole				Applied topically
	Am B cream				Applied topically

Source: Greene 1990, Chaps. 63–72.
Note: A n B = amphotericin B; ITZ = itraconazole; KTZ = ketoconazole; FLZ = fluconazole; 5–FC = fluorocytosine.
[a]Fluconazole not effective, not recommended.
[b]Itraconazole may replace ketoconazole therapy.
[c]Human studies suggest itraconazole and fluconazole to be as effective as ketoconazole-amphotericin B combination therapy.
[d]More rapid cerebrospinal fluid sterilization occurs with amphotericin B-5-fluorocytosine therapy than with fluconazole.
[e]Itraconazole not effective in nasal aspergillosis.

Table (40)

Antiviral drugs of potential veterinary importance (in most cases doses are experimental, necessitating further clinical study)

Drug	Preparation	Brand (manufacturer)	Route	Dosage	Interval (hr)
Idoxuridine	0.1% ophthalmic solution	Herplex Liquifilm (Allergen); Stoxil (SKF)	Ocular, topical	1 drop	5–6
	0.5% ophthalmic ointment	Stoxil (SKF)	Ocular, topical	Ointment	1–2
Trifluridine	1% ophthalmic solution	Viroptic (Burroughs Wellcome)	Topical	1 drop	2
			IV	1.5, 2.9 mg (humans)	4–8, 4
Vidarabine	3% ophthalmic ointment	Vira-A (Parke-Davis)	Ocular, topical	1 cm ointment	5–6
	200 mg/mL suspension for injection		IV	10–30 mg/kg	24 as a continuous drip for 12–24 hr
Ribavirin	6 g/100 mL vial powder	Virazole (ICN Pharmaceuticals)	Inhalation	Using SPAG-2 nebulizer only	8–18 hr period daily
Acyclovir	5% cutaneous ointment	Zovirax (Burroughs Wellcome)	Topical	Cover lesion adequately	3 hr, 6 times/day
	200 mg capsules or tablets 200 mg/5 mL suspension		PO	200 mg (humans)	4 hr, 5 times/day
	500 mg/vial powder		IV	250–500 mg/m^2	8 (infused over at least 1 hr)
	1 g/vial powder			5–10 mg/kg (humans)	8
Ganciclovir	500 mg/vial powder	Cytovene (Syntex)	IV	2–5 (humans)	8–12
Zidovudine	100 mg capsules	Retrovir (Burroughs Wellcome)	PO	100–200 mg (humans) 10–20 mg/kg	4
	Syrup 10 mg/mL		PO	200 mg (humans)	4
	10 mg/mL single-use vial		IV	1–2 mg/kg	Infused over 1 hr
Foscarnet			IV	60 mg/kg	8 (CMV initiation therapy)
				90–120 mg/kg	24 (CMV maintenance therapy)
				40 mg/kg	8 (for HSV and VZV infections)
Amantadine	100, 500 mg capsules	Symmetrel (Dupont)	PO	100 mg total (humans)	12–24
	Syrup 10 mg/mL		PO	100 mg total (juveniles)	24
Rimantadine		Flumadine	PO	200–300 mg total (humans)	24
				100–200 mg total (juveniles)	24
Interferon-α_{2a}	3×10^6 IU/vial	Roferon-A (Roche)	SC, IM	3×10^6 IU (humans)	24
Interferon-α_{2b}	3×10^6 IU/vial	Intron A (Schering)	SC, IM	3×10^6 IU (humans)	24

XV.V. Pharmacology of Anthelmintics

- **Definition & characteristics**
- **Classification**
- **Anti-Nematodals**
- **Anti-Cestodals**
- **Anti-Trematodals**

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ANTHELMINTICS

Def: Are the drugs that are used to control the animal parasites.

Characteristics of the ideal anthelmintic:

- Should have a broad spectrum of activity against mature and immature parasites (including hypobiotic larvae).
- Be easy to administer.
- Inhibits re-infection for extended periods of time.
- Have a wide margin of safety and be compatible with other compounds.
- Does not require long withholding periods because of residues.
- Be cost effective.

Classification

A. According to the group of parasite affected into: antinematodal, anticestodal, and antitrematodal anthelmintics.

B. According to the anthelmintic action into: parasiticide, larvicide and ovicide.

C. According to the mode or site of action into: neuromuscular pathway, metabolic pathway and reproductive pathway.

D. According to the relative toxicity to the host into:

Levamisole, pyrantel > organophosphates > benzimidazoles, endectocides

Anti-Nematodals

Antinematodals are the drugs that combat the round worm in the gut, respiratory tract, the eye and kidney including the migrating larvae in the other systems.

Antinematodals are classified according to the chemical structure into:

1. Benzimidazoles
2. Probenzimidazoles
3. Imidazothiazoles: tetramisole and levamisole
4. Tetrahydropyrimidines
5. Macrocyclic lactones (macrolide endectocides)
   i. Avermectines
   ii. Milbemycines
6. Organophosphates
7. Heterocyclic (miscellaneous) antinematodal compounds
8. Heartworm adulticides

1. Benzimidazoles

2. Probenzimidazoles

They are chemically related group of chemicals that doses not only have **anthelmintic** effect but some of them have **antifungal**, **antibacterial** and even my be **antineoplastic** effect. The first BDZ is thaiabendazole that is still present in the market for human and animal use.

Members:

Thiabendazol (thiabenzole®) albendazole (Albex®), fenbendazole (panacur®), flubendazole, mebendazole, oxifendazole (systamex®), parbendazole, triclabendazole and thiophanate (nemafax®). And the proBMZ are Netobimin (hepadex®) and Febantil (bayverm®).

MOA:

Inside the cell, they are converted into methyl-benzimidazoles that interfere with the energy utilization by the parasite's intestinal cells (inhibit the glucose uptake) through inhibiting the formation of the **β**- tubulin that is needed for the absorption of nutrients) and inhibition of fumarate reductase enzyme leading to flaccid paralysis.

PK:

- Limited amount of the drugs is absorbed from the GIT except for thiabendazole, albendazole and oxifendazole. As the members have variable solubility, their absorption is variable from the GIT.
- Plasma levels never greater than 1% of the dosed amount.
- The majority of the group except **thiabendazole** is excreted **unchanged** in feces.
- **NB:** it is better to give BMZs in low repeated doses instead of giving a large single dose as the strategy of the anthelmintic action of BMZs depends on how long the contact is more than on how much the concentration is (look up for the mode of action, it causes starvation of the parasite).

Spectrum

- They have anthelmintic, larvicidal, and ovicidal effects against a wide spectrum of round worms (GIT and lung ones). Triclabendazole specifically is a potent drug against mature and immature liver flukes.
- Many of them have antibacterial and antifungal effect like thiabendazole.
- Albendazole is approved for giardiasis in dog and cat.
- They have larvicidal and ovicidal effects.
- Due to development of resistance, and appearance of more efficient drugs, their use is decreasing.

- Their efficacy is high in ruminants and horse due to the prolonged contact with the parasite in the rumen and cecum.
- Now a day benzimidazoles are applied in sustained release devices that give extended release that ranges from 3 weeks up to 140 day according to the preparation.

Activity:

Cattle: benzimidazoles remove the major worms in the GIT and respiratory tracts including *Ostertagia, Oestrus, Cooperia, Nematodirus, Oesophagostomum* and albendazole, fenbendazole and oxifendazole are used for liver flukes. Netobimin (the pro-albendazole) is not only effective against the major GIT nematodes and the hypobiotic form of Ostertagia, but also against cestodes and Fasciola hepatica.

Horse: they are active against small and large *Strongyles, Oxuris* and *Trichostrongyles* and larger doses are needed for *S. valgaris*.

Sheep: cambendazole is effective against *Monesia spp*. besides its effect against the same species in cattle.

Dogs and cats: for ascarids, hookworms, whipworms, and the protozoal disease giardiasis in three to five consecutive daily dosage.

NB: Febantel is the only approved BMZ for cats.

Safety and side effects

- In general BMZ are safe with a wide therapeutic index that may reach 150 (remember the mode of action!).
- BMZ are combatable with most of the drugs without undesirable interactions.
- Some of them (thiabendazole, albendazole, oxifendazol and oxibendazole) have teratogenic effect in experimental animals, so should not be given for pregnant females.

- Hepatotoxicity may occur in dogs due repeated administration.

3. Imidazothiazoles

Members: levamisole and butamisole (derivative of levamisole).

MOA:

- At low dose they cause paralysis of the worm by persistent depolarization of the autonomic ganglia of the worm.
- At high doses they lead to death of the worm by starvation due to inhibition of fumarate reductase and succinate oxidase enzymes.

PK:

- Levamisole is absorbed from the gut after oral dosing and through the skin after dermal application.
- Although bioavailabilities are variable in different animals, it is well distributed throughout the body.
- Levamisole is primarily metabolized in the liver with less than 6% excreted unchanged in the urine.
- Metabolites are excreted in both the urine (primarily) and feces. Levamisole slow-release boluses are available in some countries and contain 22.05 mg/kg levamisole. They release 2.5 mg/kg during the first 24 hr and the remainder over a 90-day period.
- From the strategy of levamisole as anthelmintic, it is dependent on the concentration not the period of contact so it is administered for one single dose that is repeated after 14 days.

Anthelmintic activity:

- Commonly used in cattle, sheep, pigs, goats, and poultry to treat nematode infections.
- It has no activity against flukes and tapeworms.

- It is normally administered PO or SC, and efficacy is generally considered equivalent with either route.
- Topical preparations (over the skin) for cattle have been developed.
- In ruminant:, levamisole is highly effective against the common adult GI nematodes and lungworms and some larval stages.
- It lacks efficacy against arrested larvae, such as those of *Ostertagia ostertagi.*
- In swine levamisole, similar to the benzimidazoles, is highly effective against adult swine nematodes and some of the larval stages, but not effective against *Trichuris suis* (whipworm).
- Poultry: although not approved for poultry it is used out of label as it removes 99% of the main intestinal round worms (Ascaridia, Hetrakis, Capillaria) and the tracheal worm (Syngamus).
- Immunomodulatory acativity: Levamisole has immunostimulant effect by restoring suppressed host immunity by enhancing the interferon activity.
- Contraindications/Precautions:
- Contraindicated in lactating animals (not approved).
- It should be used cautiously or not used at all in severely debilitated animals.
- Not used in significant renal or hepatic impairment.
- Used cautiously or, preferably, delay use in cattle that are stressed due to dehorning or castration.
- Should not be given at the same time with nicotinic effect like drugs (e.g., pyrantel, morantel, diethylcarbamazine), or cholinesterase-inhibitor drugs (e.g., organophosphates, neostigmine) as they could theoretically enhance the toxic effects of levamisole.

Adverse Effects/Warnings:

- In cattle includes muzzle-foaming or hypersalivation, excitement or trembling, lip-licking and head shaking.
- These effects are generally noted with higher than recommended doses or if levamisole is used concomitantly with nicotine like effect drugs.
- When injecting into cattle, swelling may occur at the injection site that will be relieved in 7-14 hrs.
- Because of its narrow margin for safety and limited efficacy against many equine parasites, levamisole is not generally used in horses.

4. Tetrahydropyrimidines

Members: Pyrantel and Morantel

MOA:

Depolarizing neuromuscular blocking agent in susceptible parasites, thereby paralyzing the organism. The drug possesses nicotine-like properties and acts similarly to acetylcholine. Morantel also inhibits fumarate reductase in Haemonchus spp.

PK:

- Pyrantel pamoate is poorly absorbed from the GI tract, thereby allowing it to reach the lower GI in dogs, cats and equines.
- Pyrantel tartrate is absorbed more readily than the pamoate salt.
- Morantel is slower than pyrantel in its onset of action, but is approximately 100 times as potent.
- Absorbed drug is rapidly metabolized and excreted into the urine and feces.

Spectrum:

- Dogs: ascarids (Toxocara canis, T. leonina), hookworms (Ancylostoma caninum, Uncinaria stenocephala) and stomach worm (Physaloptera).

Although not approved for use in cats, it is useful for similar parasites and is considered to be safe to use.

- Horses: Pyrantel is indicated (labeled) for the removal of the following parasites in Strongylus vulgaris and equinus., Parasacaris equorum, and Probstymayria vivapara. It has variable activity against Oxyuris equi., S. edentatus and small strongyles. Pyrantel is active against ileocecal tapeworm when used at twice the recommended dose.
- Cattle and sheep: the drug is effective (as the tartrate) for the removal of the following parasites: Haemonchus spp., Ostertagia spp., Trichostrongylus spp., Nematodirus spp., Chabertia spp., Cooperia spp. And Oesophagostomum spp.
- Swine: Pyrantel tartrate is indicated (labeled) for the removal or prevention of the following parasites in: large roundworms (Ascaris suum) and Oesophagostomum spp.. The drug also has activity against the swine stomach worm (Hyostrongylus rubidus).
- Morantel tratrate: is indicated for GIT worms of the cattle at dose 10 mg/kg.

Countraindications:

Tetrahydropyrimidins are not recommended at the same time of the nicotine like actions drugs (see above for the list).

Safety and toxicity:

- Wide safety margin.
- Not indicated for young cattle.
- Safe to use in pregnant animals.

5. Macrocyclic lactones (macrolide endectocides)

A. Avermectines: ivermectin, abamectin, doramectin, eprinomectin and selamectin

B. Milbemycine: milbemycine oxyme and moxidectin

From the name endo means internal and ecto- means external that means working against both internal and external parasites including the hypobiotic larvae of the worms.

MOA:

- Old theory: GABA stimulant (the post synaptic inhibitory transmitter).
- New theory: stimulate the glutamate gated chloride channels.
- GABA and glutamate receptors are very close anatomically in the nematode neurons and arthropods skeletal muscles, they have GABA effect in high dose.
- Do not have either antitrematodal or anticestodal effects (the receptor does not occur in the flukes and tapeworms).

PK:

- Well absorbed when administered PO, parenterally, or as pour-on formulations.
- Extensively distributed in the body and concentrate particularly in adipose tissue, regardless of the route of administration.
- Of long effective concentration that is 2-4 weeks and metabolized in the liver.
- The withdrawal time (WT) of macrocyclic lactones administered SC may be influenced by the body condition of the animal (stored in the adipose tissue).
- The WT may reach 35 days as ivermectin or zero as eprinomectin in cattle.

Therapeutic activity:

IVERMECTIN

- Cattle: at dose of 0.2 mg/kg is effective for 2-4 w for protection of most of the GIT nematodes and lung worm.
- Horse: 99-100% effective against large Strongyles, Ascarids, thread worms, lung worm, horse bots (Gastrophylus), Microfilariae, Draschia and Habronema (summer sore). Note that you may get skin reaction when it kills the migrating summer sore larvae so it needs additional anti-inflammatory treatment after one month of ivermectin therapy.
- Swine: 100% effective against GIT, lung worms and kidney worm
- Dogs and cats: highly effective against immature heart worm and most of the canine nematodes.
- Birds: give absolute success for the major intestinal nematodes (Ascaridia, Capillaria and Hetrakis).
- All animals and even trees: highly effective against the animal ectoparasites and parasites of the trees.

ABAMECTIN: is the precursor of ivermectin used mainly in agricultural fields and for household for the house insects.

DOARAMECTIN: besides its excellent antinematodal and insecticidal effect it has unique effect against *myiasis* (depterous fly infestation).

EPRINOMECTIN (ivomec eprinex®): mainly approved for cattle for GIT nematodes, lung worm and ectoparasites. *Some more advantages which are that it is not extensively metabolized and excreted from the kidney that would help more in treating the kidney worms and it does not need any time for withdrawal.*

SELAMECTIN (revolution®): mainly approved for dog and cat for prevention and treatment of heart worm and for fleas and other ectoparasite.

MILBEMYCINE (interceptor palatab®) is approved as chewable tablets for heart worm in dogs and cats

Safety and toxicity:

- This group works on the glutamate gated chloride channels and the GABA receptors which are present in the CNS of mammals and the members do not cross the BBB except in the collie breed of dogs so they are definitely safe for mammals except collie dogs.
- Symptoms of toxicity includes listlessness, mydriasis, ataxia, coma. Picrotoxin is not an effective antidote.

6. Organophosphates

(Dichlorophos, Comaphos, trichlorophos, haloxone, metriphonate)

- This group was first used as insecticide with external use only.
- Eventually it was found they have antinematodal effect.
- They have a narrow spectrum.
- The only one that is approved now, is dichlorophos (Task®).
- Dichlorophos is approved for horse, dog, cat and pig.

MOA: by non-reversible binding to the cholinesterase enzyme (find out the effect of acetyl choline accumulation in the living body).

PK: given in resin pellets that give 50% of the drug in 24 hours and the rest goes to the intestine in contact with the nematode.

Therapeutic spectrum: in dogs and pigs it is effective against the nodular worm, whipworms and hookworms but not the migrating larvae. In **horses** mainly for bots and pinworms.

Adverse effects:

- Acute form: salivation, defecation, miosis and ciruling

- Chronic form: chronic neurotoxicity due to demyelination of the nerve axons.

Contraindications: not to be given concurrently with the drugs of nicotine like effect *(find it out).*

7. Heterocyclic compounds

Phenothiazine:

- Was the first discovered antinematodal drug.
- Its mode of action is by inhibition of glycolysis (inhibition of carbohydrates metabolism) in the worm.
- It is effective mainly against the stomach worms.
- It is not popular in the market any more due to its hemoglobinurea and photosensitizing effects and the anthelmintic resistance.

Piperazines:

- Is a widely used anthelmintic.
- The mode of action is by stimulation of GABA receptors in the worm leading to flaccid paralysis.
- By paralyzing the worm it could be expelled by the intestinal movement.
- Some of it is metabolized in the liver and the remainder excreted unchanged in the urine.
- Used mainly for the ascarids species in all animals and the pinworm in horse.
- Of wide safety margin.
- The only limitation is the liver and kidney diseases.

Diethylcarbamazine (DEC):

- A derivative of piprazine.

- Effective mainly against immature heartworm.
- Is given for dogs on daily bases as preventive medicine for heartworms larvae during the season of mosquitoes.
- Considered safe except for some sensitivity for some individuals.

8. Heartworm adulticides

To overcome the heartworm in dogs and cats, it needs a plan to cut off on the worm life cycle. That could be through one or more of the next steps:

- Killing the adult worms: using adulticides like thiacetarsamide and melarsomine (used in dogs only, adult worm removal in cat need surgery).
- Killing the larvae: using microfilaricides and larvicides like ivermectin, milbbemycin and DEC.
- Killing of the intermediate host, mosquitoes.

ADULTICIDES

Thiacetarsamide (caparsolate):

- Arsenical compound.
- Given orally, metabolized in the liver and excreted in the kidney.
- Of low safety margins.

Adverse reactions include:

- Tissue sloughing if escaped extravascular tissues.
- Vomiting and diarrhea due hepatotoxicity and renal toxicity.
- Thromboembolism as the dead worm clog the pulmonary veins.

Melarsomine (immiticide):

- Arsenical compound.
- Safe for intramuscular administrations

ANTICESTODALS

Background:

- Taeniauges are the drugs that cause paralysis of the tapeworm and they need purgative to accompany it.
- Taeniacides are the drugs that are able to kill the worm completely and detach the scolex.
- To control the tape worm it necessitates the control of the intermediate host too.

Organic old fashion taeniafuges:

- Parts of natural plant like pumpkin seeds, pomegranate roots and ginseng flowers.
- Extracted materials like arecoline, nicotine sulphate and turpentine.

MODERN TAENIACIDES

DICHLORPHEN (taeniathane®):

- Antehlmentic, antifungal and bacteriostatic
- Still used in dogs and cats in combination with toluene (vermiplex®) for tapeworm and roundworm.

RESORANTEL(terenol®):

- For Moneizia in sheep and rumen flukes in cattle. Produces its action by inhibition of glucose utilization.

BITHINICOL, BITHIONOL (bithin®):

- Still used for Dipylidium, Echinococus and Taenea in dogs and Raillietina in poultry.
- Interferes with glucose metabolism

BMZ:

- Mebendazole, fenbendazole, oxfendazole, and albendazole effective against Taenia, Moneizia and Ecninococus but not Dipylidium.

- Mebendazole and albendazole are used successfully for the control of hydatid cyst in human

Praziquantel (Droncit®) and Epsiprantel (cestex®):

- Effective against all kinds of tapeworm
- With limited effect on hydatid cyst
- MOA is by increasing the C ions influx in the worm leading to its irreversible paralysis then the worm is digested.
- Now approved for dogs, cats and pet birds but its use in large animal is not feasible in Egypt.
- Internationally there are many combinations of praziquantel with other antinematodal or antitrematodal drugs (equimax paste®)for horses contains ivermectin and praziquantil, (quest plus gel®)for horses contains moxidictin and praziquantil and (Iverhart Max®) for dogs contains ivermectin, pyrantel pamoate and praziquantel
- Side effects include: vomiting, salivation, diarrhea, and lethargy but no teratogenic effect

ANTITREMATODALS

- The trematodes of interest are Fasciola (liver flukes), Paramphistomum (rumen flukes) and Paragonimus (lung flukes of dogs and cats).
- To stop the attack of flukes it needs killing of the worms inside the animal body and prevention of infection by controlling the intermediate host, the snails (by using molluscicides).
- The main focus internationally is on the fasciolocides.

Old fasciolocides

Carbon tetrachloride:

- Was the first drug to be used against adult flukes in sheep.
- Dangerous for cattle.
- Withdrawn from the flukicides list due its sever toxicity

Side effects include:

- Fatty liver
- Hypocalcimia

Its toxic effects are aggravated in cases of:

- Debility
- Feeding high protein ration
- Calcium deficiency
- Lactation
- To avoid the toxic effect one should give external source of calcium and antioxidants and avoid high protein ration

Hexachloroethane:

- Less toxic than carbon tetrachloride.
- Was used in sheep and cattle.
- Cause milk tainting.
- Cause loss of appetite.
- High protein ration predisposes for its toxicity.

NEW FASCIOLOCIDES

Albendazole:

- Is approved for liver flukes in cattle.
- Requires 27 days withdrawal time.
- Not for pregnant animals due to its teratogenic effect.

Rafoxanid:

- Approved for fasciolosis and haemonchosis in cattle and sheep.
- The mode of action is by proton ionophore as it increases the cations influx in the cell that interferes with the energy production.

Praziquantel:

- Approved for flukes in dogs but it is too expensive to use in ruminants (see details about the drug at the anticestodal section)

Clorsulon (curatrem®):

- Is the most effective fasciolocide
- Effective (100%) against both mature and immature stages
- Clorsulon is rapidly absorbed into the bloodstream and a big portion of it is bound to RBCs.
- When *Fasciola hepatica* ingest it (in plasma and bound to RBC), they are killed as the glycolysis is inhibited and cellular energy production is disrupted.
- There is a good combination of ivermectin and clorsulon for cattle (ivomec-super®) that protects the animal from the liver flukes, GIT worms, lung worm, and ectoparasites.

MOLLUSCICIDES:

- Cupper sulphate at rate of 10kg/feddan and sodium pentachlorophenate at rate of 4 kg/feddan are effective for prevention of snails from growing in the pasture.

Table (41)

Names and formulas of benzimidazole anthelmintics

Compound	Trade name	Chemical name	Structural formula
Albendazole, INN	Valbazen	Methyl [5-(propylthio)-*H*-benzimidazole-2-yl] carbamate	$CH_3CH_2CH_2$—S— ; NH—C(=O)—O—CH_3
Fenbendazole, INN	Panacur Safeguard Axilur EnProAl	Methyl 5 (phenylthio)-2-benzimidazolecarbamate	—S— ; NH—C(=O)—O—CH_3
Flubendazole, BAN	Flubenol	Methyl [5-(4-fluorobenzoyl)-1*H*-benzimidazole-2-yl] carbamate	F— ; —C(=O)— ; NH—C(=O)—O—CH_3
Mebendazole, INN	Telmin Telmintic Vermox (USSR) Multispec Ovitelmin Mebenvet	Methyl 5-benzoyl-2-benzimidazole-carbamate	—C(=O)— ; NH—C(=O)—O—CH_3
Oxfendazole, INN	Benzelmin Systamex Synanthic	Methyl 5(6)-phenylsulfinyl-2-benzimidazole-carbamate	S=O ; NH—C(=O)—O—CH_3
Oxibendazole, INN	Anthelcide EQ Lodiac	Methyl-5-*n*-propoxy-2-benzimidazolecarbamate	$CH_3CH_2CH_2O$; NH—C(=O)—O—CH_3
Parbendazole, INN	Verminum Worm Guard Helmatac	Methyl 5-butyl-2-benzimidazole-carbamate	H_9C_4 ; NH—C(=O)—O—CH_3
Thiophanate, BAN	Nemafax	1,2-bis(3-ethoxycarbonyl-2-thioureido)benzene	$NHCSNHCOOC_2H_5$ $NHCSNHCOOC_2H_5$

Note: → denotes position of carbon 5 in structural formula.
INN = international nonproprietary name; BAN = British approved name.

Table (42, 43)

Nitroimidazoles

Name	Chemical name (Empirical formula) [Molecular weight]	Chemical structure
Dimetridazole	1,2-dimethyl-5-nitro-1*H*-imidazole ($C_5H_7N_3O_2$) [141.13]	
Ipronidazole	1-methyl-2-(1-methylethyl)-5-nitro-1*H*-imidazole ($C_7H_{11}N_3O_2$) [169.18]	
Metronidazole	1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole ($C_6H_9N_3O_3$) [171.16]	
Ronidazole	1-methyl-2-[(carbamoyloxy)methyl]-5-nitroimidazole ($C_6H_8N_4O_4$) [200.16]	
Tinidazole	1-[2-(ethylsufonyl)ethyl]-2-methyl-5-nitro-1*H*-imidazole ($C_8H_{13}N_3O_4S$) [247.26]	

Arsenicals

Name	Chemical name (Empirical formula) [Molecular weight]	Chemical structure
Carbarsone	[4-[(aminocarbonyl)amino]phenyl]-arsonic acid ($C_7H_9AsN_2O_4$) [260.07]	
Nitarsone	4-nitrophenylarsonic acid ($C_6H_6AsNO_5$) [247.04]	
Roxarsone	4-hydroxy-3-nitrophenylarsonic acid ($C_6H_6AsNO_6$) [263.03]	

Fenbendazole
($C_{15}H_{13}N_3O_2S$)
[299.35]

Albendazole
($C_{12}H_{15}N_3O_2S$)
[265.33]

XV.VI. PHARMACOLOGY OF ANTI-PROTOZOALS

- **Definition & characteristics**
- **Antibabesial drugs**
- **Antianaplasmosis**
- **Antitrypanosomal drugs**
- **Antihistomoniasis drugs**
- **Antispirochaetal drugs**
- **Anticoccidial drugs**

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Antiprotozoal drugs

Parasitic protozoa are responsible for a wide range of diseases in both animals and man. Theses diseases are difficult to eliminate as ticks, tsetse files and tabanids that abound in many of the under-developed parts of the world frequently transmit them.

Protozoal diseases are classified into:

1- **Blood protozoal diseases** in which the infective protozoa habitats in blood.

2- **Babesia** (babesiasis) and **theileria** or **anaplasma** (theileriasis or anaplasmosis) which are living in the red blood corpuscles.

3- **Trypanosoma** (trypanosomiasis), **histomonas** (histomoniasis) and **spirochete** or **rickettsiae** (spirochetosis or ricjettsiosis) are found in the blood plasma.

2- Tissue protozoal diseases

In which the infective protozoa habitats certain tissues other than blood as coccidian and amoebae.

I- ANTIBABESIAL DRUGS

- Babesiasis (Tick fever or piroplasmosis) is transmitted by ticks and the parasites multiply into the red blood corpuscles which are ruptured and produce hemolytic anemia and fever.
- Eradication of ticks is necessary for preventing transmission of the dispenses and that done by insecticide.
- Antibabesial drugs include:

1- Quinuronium sulphate (Acaprin®, Babesan®, Diveronel®).

This is urea compound, it is a white to yellow powder with a bitter taste that is usually marketed as table 5% aqueous yellow solution. Effective against babesia in all animals.

Action and uses.

The drug is used in *Babesia caballi* infections (biliary fever) in horses, *B. bovis* and *B. bigemina* infections in cattle (bovine redwater and Texas fever), *B. ovis* and *B. motasi* in sheep and *B. canis* (biliary fever or malignat jaundice) in dogs. If the drug is used in the early febrile stages of the disease, clinical cures can be achieved in 24 to 48 hours, though a second injection may be needed on the next day or the one after.

The course of treatment should not be repeated for a period of at least 2 weeks, but preferable 3 months: this is due to the occasional development of sensitization, which result in sever shock and death.

Dosage:

Horses 0.3-0.5 mg/kg.

Cattle, sheep and pigs 0.5mg/kg.

Dogs 0.25 mg/kg.

Solution of 5% should be given s.c. only in the tail fold in all species except the sheep and dog (should be diluted 10 times to give 0.5% concentration.

It is given subcutaneously only for 2-3 days and cure occurs within 2 days.

Atropine is given with it as it has anticholinestrase effect and cause depression of the heart.

N.B it stimulate release of histamine (Allergy and pain at site of injection)

- It must not be repeated before one month.

Toxicity:

Toxic reactions are similar for quinapyramine, with muscle tremors, salivation, urination and defecation: these symptoms may persist for 6-10 hours. Sever shock with a rapid fall in blood pressure, and result in sudden death may also occur.

2- Imidocarb dipropionate (imizol)®

Action and uses:

- This drug is used for the treatment and prophylaxis of babesiasis and anaplasmosis in cattle.
- It is given by S.c or I.M injection.
- It has anticholinestrase effect, so atropine is administered with it.

Dosage:

Imidocarb is given S.C. or by i.m. injection.

Cattle 1.2 mg/kg b.wt., horses 2.4 mg/kg. b.wt. and dogs 6 mg/kg b.wt.

The prophylactic dose for babesiasis in cattle is up to 3-mg/kg b.wt. this gives protection for almost 1 month.

Saftey and toxicity:

It has been suggested that at 10 mg/kg b.wt. in cattle Imidocarb can cause death. The safety margin is therefore not high and animals should be withheld from slaughter for up to 28 days.

3- Diminazene aceturate (Berenil)®

It is complex compound odorless yellow powder which soluble in water (1:14) but slightly soluble in organic solvents.

Action and uses:

Its **trypanocidal, babesicidal and bactericidal** (mainly *Brucella* and *Streptococcus* species). As a trypanocide, Berenil® is effective against *T. vivax* and *T. congolense* but less effective against *T. brucei* (necessitating a large dosage ratet).

Dosage

Berenil® consists of 8.75% phenazone and 7% diminazene aceturate and it administered by i.m. or s.c routes within 5 days of preparing the solution (or if stored in a refrigerator 14 days).

For babesia and trypanosome (*T. vivax* and *t. brucei*) infections, single doses at rate of3.5 mg/kg b.wt. should be adequate in horses, cattle, sheep and dogs. Disappearance of symptoms may be expected within 24 hours. Berenial® has a limited prophylactic action and produce a local reaction at the site of injection: they may be severe in hours.

4- Phenamidine Isothionate:

It is used for treatment of babesia infection in cattle, hours and dogs. It produces its action by interfering with synthesis of DNA in the parasite.

It is used to the treatment of babesia infections in cattle, hoarse and dogs.

It is administered s.c to houses and cattle in doses of 0.03 mg of a 40% solution per kg b.wt. and to dogs at the rate of 0.3mg of a 5% solution per kg b.wt.

Single doses are used usually sufficient and rapid in cattle, but it may repeat after 5-6 days in canine babesia infections.

5- Amicarbalide isothionate (Diampron)®

It is complex urea compounds and is related to quinronium sulphate.

Action → it produce its action by interfering with synthesis of DNA of parasite.

Actions and uses:

It is active against *B. divergen, B, bovis, B. bigemina, B. argentina* and *B. caballi.* It is used mainly to create premunity by controlling the clinical symptoms but not eradicating the infection.

This compound is much less toxic than quinuronium sulphate (its LD_{50} is 15 times that of acaprin), so has better effects.

Dosage:

The compound is administered by s.c., i.m. and slow i.v. injection, preferably at the high fever and the second dose may be given 24 hours after the first. A dose varies between 5 and 10 mg per kg body weight. Local swelling at the sites of s.c and i.m. injections may be seen due to its histamine releasing.

6- Trypan blue:

It is a bluish-grey, water-soluble powder that in solution gives a blue-violet colour and is one of the azo. It used against the babesias, but is

ineffective against *B. equi, B. bovis* or *B. gibsoni.* The drug is relatively non-toxic but stains tissues and secretions, including milk, a blue-green colour that may persist for several weeks.

Dosage:

The drug should be freshly prepared and given at body temperature in concentration of 1-2% and was given by i.v. injection only at: Horse and cow 1-4 g; sheep 0.5-1g and dog 20-150mg.

II- ANTI-ANAPLASMASIS

1- Tetracyclines:

It is useful for treatment and eradication of the carrier state (given i.m. or i.v.for 10 days).

2- Dithiosemicarbazones:

It injected i.v. for10 days and can eliminate the parasite completely.

Combination of dithiosemciarbazones and oxytetracycline reduce their toxic effects.

3- Imidocarb dipropionate (Imizol®):

Imidocarb 3 s.c. or i.m. injections with 24 hours interval has a good results. The dose was given in cattle 3 mg/kg b.wt.

III- ANTITRYPANOSOMAL DRUGS

Trypanosomiasis (sleeping fever) are one of the common diseases in tropical countries that infest camel, horse, cattle, buffaloes and dogs. Tse-tse files (glossina) transmit it. Treatment should be in early stages before the parasites enter CSF as the drugs cannot reach CSF fluid in effective concentrations.

1- Quinopyramine campound (Antrycid)®:

- It is a yellow powder soluble in water, it is atryponocidal drug for prophylactic and treatment of trypanosomiasis in animals given intravenously.

Sulphate → slowly absorbed so prolonged action → used as prophylactic

Chloride → has short rapid action → used as curative.

- **This prosily is better** → (2 parts Q. chloride + 3 parts Q. methyl sulphate).
- Some toxic effects may produce after administration of this drug due to its histamine-releasing effect and anticholinestrase action e.g ↑ salivation, sweating, tremors, even loss of consiousness and sometimes death 2-6 hrs after injection.
- The local reaction is serious → so it is advisable to divide the dose and inject it in 2 or 3 different sites.
- Atropine sulphate → injected before it.

Action and uses:

Quinapyramine is active against most trypanosomes. The action is attributed to the inhibition of growth and cell division.

Sulphate and chloride prophylactic mixture (3 parts sulphate and 2 parts chloride), is administered s.c. at rate of 0.025 ml/kg b.wt./each animal. The protection was about of 90 days interval in the breeding season of stallions. Protection against *T. congolense* in cattle was about of 230 days. Suramin will considerably increase the protective power of quinapyramine.

2- Phenanthridium compounds:

(d) Dimidium bromide → show delayed toxic effects.

(e) Homidium bromide → less toxic rapidly eliminated from body. It results in transient liver damage and local reaction by sc or I.M injection while I.V injection is dangerous. It is rapid in its action and acts prophylactically for one month.

Dose →1% solution given 0.25-1 mg/kg.

(f) prothridium

It is used for prophylaxis given sc or I.M acting for 6-8 months at it is bound to plasma proteins then execrated in the bile.

(g) **Metanidium bromide.** It is introduced for its prophylactic properties. These properties are due to its deposition at the site of injection with slow absorption (6-8 months are prophylactic period).

Mode of action of phenanthridiniums is unknown but suggested that stop the multiplication of trypanosome.

Dose I mg/kg b.wt.

3- Diamidines compounds

Action → Trypanosomes require great need of glucose for their activists and so the drug related to its hypoglycaemic action.

- Theses compounds have activity against (babesia & trypanosomes) and has some antibacterial activity.

Examples:

Phenamidine & pentamidien & propamidine and diminazene.

- **propamidine and pentamidine:**

Which are retained in the body for long time due to its fixation in liver.

(2) Diminazine aceturate (Berenil)®:

- It is atrypanocide, babesiocide and bactericide especially against brucella and streptococci.

- A single dose cure within 24 hrs and it is given by s.c or IM but produce local reaction at injection site.

N.B)

- It is given with atropine as it depresses the heart.
- It is used to treat early acute cases of trypanosomiosis.

4- Prophylactic complexes:

Suramin (Naganol)® or (antrypol)®

- It is an old trypanocidal drug used as prophylactive and curative drug for acute trypansomiasis in large animals.
- It is given as a single dose I.V but not I.N as it is irritant.
- It is combines with the plasma proteins and persists for many weeks in the body.
- The acidic suramin can be combined with other basic trypanocidal substances to form after injection insoluble complexes (depots) from which absorption become slowly.
- These complexes are of value in prophylaxis **Ex** surmain-homidium which produce protection for 7 months.

N.B

Suramin used as synergistic potentiator of the phenanthridium derivatives.

Dosage:

Therapeutic dosage is: horse (7-10 mg/kg), camel (8-12 mg/kg) and cattle (12 mg/kg). The dose in horses may be repeated to three times at weekly intervals. The drug is given as a 10% solution.

Safety and toxicity:

Suramin is potentially toxic, because the therapeutic index is very narrow: horses as donkeys are very susceptible, but camels are quit resistant.

- It is more effective in early (acute) stages of the disease before the parasite enter to C.N.S.
- It is less effective in chronic cases as it slightly enter C.N.S.

Action inhibiting the multiplication of the parasite.

* It has prolonged action due to:-

1) firm binding to plasma protein.

2) it is reabsorbed by renal tubules.

N.B It is acidic so it must not be given with quinuronium which is alkaline.

5- Organic arsenicals:

Trivalent compound e.g **neoarsphnamine** when injected I.V rapidly fixed by tissue and slowly excreted.

IV- ANTISPIROCHAETAL DRUGS

- Spirochatosis affects mainly horse, fowl and turkey.
- Arsenical compounds especially the organic salts **e.g.** acetarsol (orally), neoars phenamine (I.V) and sulpharphenamine (I.M).
- They act by→ inhibiting SH containing enzymes in protozoan.

V. ANTICOCCIDIAL DRUGS (COCCIDIOSTATS)

Introduction:

Coccidiosis is a parasitic disease caused by tissue protozoa (Family Eimeridae) or Emeria species. It induces partial or complete destruction of musocsal cells along the intestinal tract (Intestinal Coccidiosis) in poultry and animals and also liver cells of rabbits (hepatic Coccidiosis).

Coccidiosis causes great economic losses as it decrease body weight gain and immuno-responses. Deaths may occur following sever diarrhea associated with hemorrhage. (Cecal Coccidiosis caused by *E. tenalla* in chickens). Transmission of the parasite occurs by ingestion of sporulated oocysts.

Types of Coccidiosis:

1- Intestinal Coccidiosis:

- It infects the intestinal mucosa of chickens, rabbit and animal. **In Chickens,** it is caused by 6 stains of *Eimeria Spp.* As, *E. necatrix, E. maxima, E. acervulina, E. brunette, E. mitis and E. paracox.*

2- Ceacal coccidiosis:

- It infects ceacum of chikens and rabbits.
- It caused by *E. tenella* in poultry.

3- Hepatic Coccidiosis:

- It infects liver cell of rabbits.
- It Hepatic Coccidiosis is caused by *E. Staidae.*

Life cycle of Eimeria species

Coccidia has 2 stages in its life cycle (7 days) (Figure 54).

A- **A sexual stage** (Schizogony stage) during which the protozoan rapidly multiplies and a great number of schizonts fill the mucosal cells leading to its burst and relesing merozoytes to attack other cells.

B- **Sexual stage** (Sporogony stage) in which the capsulated zygote is formed by fertilization of macrogametes with microgamete then oocysts is formed and shed with feces and changed to sporulated oocystes (infective stage) out side in the presence of suitable temperature and humidity.

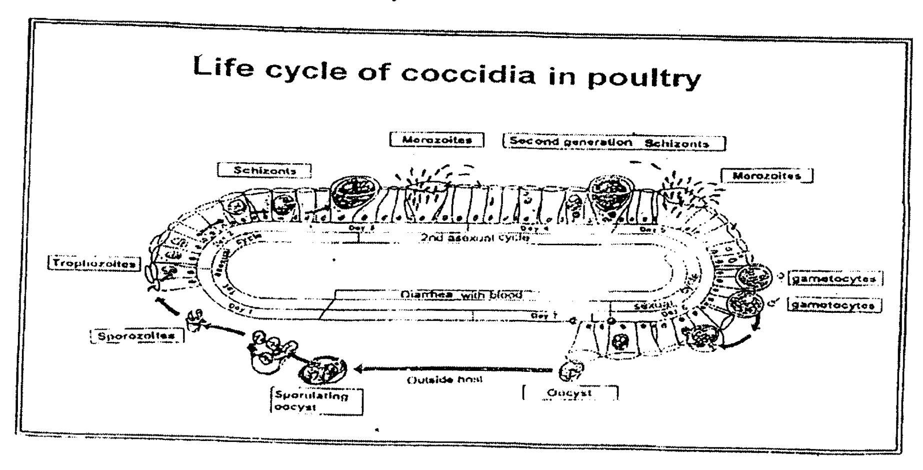


Figure (54): Life cycle of coccidian in chickens

The effect of coccidial infestation is to cause haemorrhage, destruction of cells on a massive scale and very often death. To put the magnitude of infection into perspective, it has been calculated that one oocyst of *E. bovis* ingested by a calf, may yield 24 million second-generation merozoites, and that an infection of only 1000 oocyst would lead to the destruction of 24 billion host intestinal cells.

Ideal coccidiostat should be:

1) Cheap (not expensive).
2) Active against most species of Eimeria.
3) With no residue or toxic effect on the animal.

Control of coccididosis:

1- Destruction of oocysts in poultry and rabbit houses using disinfectants, and other hygienic managements.
2- Prevention of Coccidiosis by:
   a. Immunization only in layer by:

   Natural infection with partial drug control, where natural infection is reduced to induce immunity but resistant strains are developed.

   Vaccination: using attenuated oocyst which sprayed direct on the feed or given in water. There are two preparation in the market, either 5 or n8 strains but these are not native strains and it may induce sub clinical Coccidiosis that has adverse effect on body weight gain.

   NB:

   - Broilers are not vaccinated against coccidia due to latent infection may retard growth as it developed immunity 30 days after application.
   - It is very expensive in comparison with the coast of anticoccidials.

b- prophylactic drugs: by using coccidioatat as feed additives.

3- Treatment of infected birds by suitable anticoccidial drugs.

Classification of Anticoccidials

1- Prophylactic drugs.

- They are drugs used mainly as feed additives to prevent Coccidiosis.

- They act on the extracellular stages to prevent their penetration of the cells or on the intracellular stage to stop or inhibit their development.

A- Polyether antibiotic ionophores: as Monensin, Salinomycin, Lasalocid, narasin, Maduramicin, Semaduramicin.

B- Chemical coccidiostates: as Nicarbazin, Clopidol, Methybenzquate, Amprolium, Ethopabate, Diclazuril, and haloguginone.

2- Drugs for treatment.

II- Drugs for treatment: Drugs which destroy intracellular coccidian during their growth. (late stage of second generation schizontes or on the gametocytes) eg. Sulphonamides, Amprolium, Diaveridine, Pyrimethamine, Toltrazuril and Diclazuril.

1- Prophylactic drugs

I- Polyether antibiotics (Ionophores):

- They are complex molecules isolated from various actinomyces.
- They are used as preventive or prophylactic in poultry feed in broilers or replacements.
- Ionophores have low therapeutic index and higher doses in feed may casue sides effects, intoxication so they should be mixed well with poultry feed.
- Some of members act as growth promoters e.g Monesin in cattle, salinomycin, maduramicin and semduramicin in poultry.

Ionophores can classified into:

Monovalent polyether: (Monensin, salinomycin and narsin)

Divalent polyether: (lasalocid)

Monovalent monoglycoside polyether: (maduramicin and semduramicin)

Mechanim of action:

They act by interfering with the transport of ions of K^+ and Na^+ through membranes of *Emeria*. This leads to an influx of positively charged ions (Cations) and subsequently causes upset of osmotic balance cells as well as disturbances of mitochondrial function of intracellular coccidian.

They are active against sporozoites and merozoites at the first 2 days of life cycle of *Eimeria*.

Pharmacokinetics:

Ionophores are poorly absorbed from gastrointestinal tract (GIT) following their oral administration. They have a short withdrawal time after stopping of administration. (3-4 days).

N.B: Continuous development of ionophores by modification in their chemical structure to decrease the effective dose consequently to minimize their side effects. It should be well mixed with poultry feed to subside in proper dose (Therapeutic failure) or toxicity.

Action and Uses:

- They are highly active against intestinal and cecal Coccidiosis in poultry.
- They do not interfere with immunity.
- They have growth promoting effect.

- They are used as coccidostates for prevention of cecal and intestinal Coccidiosis in broilers (Continuously in the feed) and replacement layers or breeders up to 16^{th} week of age.

Contra- indications and Toxicity:

- They should be not mixed with other anticoccidials.
- They should not given with the antibiotic "Taimulin" to prevent incidence of cardiac toxicity and deaths.
- Cardiac toxicity may (myocardial edema).
- Immunosuppersion and failure of vaccination may occur due to administration of toxic doses.
- Ionophores have a narrow ssafety margin. Therefore, they should be mixed well with poultry or animal feed.
- Lasalocid cases wetting letter.
- They are not given to layer or breeders.

Doses:

- Monensin 120 PPm
- Lsalocid 60 PPm in feed continuously
- Salinomycin 60 PPm in feed continuously
- Narsin 70 PPm in feed continuously
- Maduramycin 5 PPm in feed continuously
- Semduramycin 3 PPm in feed continuously

II- CHEMICAL ANTICOCCIDIALS

Classes:

SLPHONAMIDES:

- ***Sulphadimidine***
- ***Sulphaquinoxaline***
- ***Sulphadimethoxine***
- ***Sulphachloropyrazine***

VITAMIN-ANTAGONISTS:

- ***Amprolium hydrochloride.***
- ***Diaveridine and pyrimethamine.***

QUINOLONES: ***Methylbenzoquate and Decoquinate.***

PYRIDINES: ***Clopidol.***

GUANIDINE: ***Robenidine.***

DINITROBENZAMIDES: ***Dintolmid (Zoaline).***

BENZENE ACETONITRILES: ***Diclazuril and claszuril***

CARBANILIDES: ***Nicarbazin (Dinitro compounds)***

SYMMETRICAL TRIAZINONES: ***Tolreazuril (Bycox).***

1- Sulphonamides

Action:

Sulphonamides are the first synthetic anticoccidials used successfully in coccidiosis treatment. They possess synthetic antibacterial and anticoccidial actions. They are very effective against intestinal than caecal coccidiosis. Systemic types of sulphonamides are useful in heptic coccidiosis in rabbits.

Mechanisms of action:

Sulphonamides interfere with utilization of paraminobenzoic acid (PABA) which is essential for the formation of folic acid and subsequently the formation of ribonucleic acid (RNA) of Emeria species (coccidiostatic action). They produce their action by destroying schizonts containing merozoites.

N.B: Vitamin antagonists potentiate the action of sulphonamides because these drugs interfere with various parts of PABA-folic acid pathway.

Doses and administration in chickens:

1- Sulphadimidine sodium 0.1% for 2 days. 0.05% for 4 days, Drinking water.

2- Sulphaquinoxaline 500 PP. (0.5gram) per one liter for 7 days, drinking water.

3- Sulphadimethoxine 0.05% for 10 days. Drinking water.

4- Sulphachloropyrazine 0.03% for 3 days, Drinking water 0.5 g/liter.

Disadvantage:

They are narrow spectrum (intestinal Coccidiosis), thereforeM they must be combined with other anticoocidials as diaverdine, pyrimethamineand amprolium. They prolong blood clotting time due to interference with Vit K synthesis. Continuous feeding of cockerels on sulphonamides cause hyperplasia of semineferous tubules. Sulphonmaoide should not be used in layers because they inhibit carbonic anhydrase enzyme that is responsible for egg shell formation resulting in soft shelled eggs.

Their effects is antagonized by methionine which added to poultry rations. They are precipitated in acidic urine forming crystalurea.

Disadvantage of sulphonamide as coccidiosats:

1- They do not affect all types of Imperia species.

2- On prolonged administration they casue:

a- loss of weight

b- Thinning of egg shell, therefore they are not given for laying hens.

c- Testicular damage leading to sterility

d- Inhibit the synthesis of Vit K retarding blood coagulation or clotting.

2- VITAMIN- ANTAGONISTS:

(A) Amprolinm hydrochloride (Amprol)®

- Amprolium is chemical anticoccidial agent can be mixed with poultry feed or administered in drinking water.
- It is effective only against *E. tenella* and *acervulina,* therefore, it is used as mixture with Ethopabate which added a good effect against *E. burrnetti* and *E. maxima.* In concentration of (125PPm Amprol +4 PPm Ethpabate).
- Amprolium has been used for treatment of Coccidiosis in chickens, turkeys and ruminants.
- It is usually given combined with sulphaguinoxalline mixed with feed or added to drinking water.
- It is of low toxicity and can be given for laying hens.

Mechanism of action:

Amprolium prevents the utilization of thiamin (Vit. B_1) by Eimeria species in the early first generation schizonts and merozites.

Dosage and administration:

- ***Broilers and layers*** (0.0125%) in feed or (0.0125% or 0.05%) in drinking water for treatment for 2 weeks.

Cattle: 10mg/kg body weight for 5 days.

- Amprolium has no withdrawal time.

Action Antithiamine (Antivitamin B_1)

(B) Diaveridine and Pyrimethamine

- They are used as coccidiostates and given alone or in combination with sulpha drugs e.g. sulphadimidine, sulphaquinoxaline, sulphadimethoxine.
- They have a synergistic action with sulphonamides, where sulphonamides prevent the utilization of PABA to give dihydrofolate, and diveridine or pyrimehamine prevent conversion of dihydrofolate to tetrahydrofolate by inhibition of dihydrofolate reductase enzyme.
- It is of low toxicity and dose not affect the egg production.
- It prevents the formation of folic acid by coccidian parasite and prevents their growth and multiplication.

Action: Folic acid antagonist

(c) Ethopabate:

- It is used effectively for prophylaxis and treatment of clinical outbreaks of intestinal than cecal Coccidiosis.
- It acts on first generation schizonts by preventing differentiation of merozoites and used in combination with Amprolium.

Action: para amino benzoic acid (PABA) antagonist.

- It is effective against all types of Eimeria, Except Eimeria tenalla, usually given combined with diaverid.

3- Nitrofurans

- They are extremely effective anticoccidial drugs preferable than sulphonamides a they are:

   a) of low toxicity

   b) of great palatability

   c) do not affect the body weight

- on prolonged administration they cause male sterility.

Nittrofurans used as anticoccidial drugs:-

(1) Nitrofurazone

1. It is anitrofuran used to prevent and treat caecal Coccidiosis in chickens given mixed with food (0.005%) as it is insoluble in water.
2. Higher doses results in toxicity effects as loss of appetite, excitement, testicular damage with reversible arrest of spermatogenesis.
3. Duckling are very susceptible to its toxicity.

(2) Furazolidone (Neftin)®

1. It affects bacteria (gram(+) and gram (-) and protozoa (coccidian and trichomonas, histomonas).
2. It is given as prophylactic and curative for Coccidiosis, in chicks and rabbits mixed with feed as it is insoluble.
3. Not fed to breeding stock as may produce change in testicular tissue.

(3) Furaltadone

It is water soluble compound used for Coccidiosis in drinking water.

(4) Acinitrazole It is effective but mostly used for treat and prevent of histomoniasis in turkey. For treatment given in food 0.08% for 14 days while prophylaxis 1/2 the therapeutic use.

4- QUINOLONES:

A- Decoquinate

- It is used as premix for prevention of Coccidiosis in broiler chickens and lambs.

Dosage

Broilers 20-40 PPm in feed continuously.

Ewas and lams 100PPm in diet for 28 days.

Cattle 500 PPm in feed.

Contraindication:

- Decoquinate is unsuitable for turkeys, laying and breeding birds
- A 3 day withdrawal period is required for meet.

b- Methylbenzoquate

- It acts as coccidiostate by antagonizing the invasion of sporozoites in the first day of life cycle of *Eimeria* species.

- It is used at 8.35 PPm in a combination with clopidol for prevention of Coccidiosis in chickens and turkeys.

Dose: clopidol 100 PPm. Plus Methyl benzoquate 8.35 PPm in feed continuously.

- dequinate and methyl benzoquate act by penetrating the epithelial cells of sporozoite and kill them.
- They are insoluable so used added to feed.

5- Dinitro compounds (Carbanilides)

* Induces prophylactic coccidocidal activity against most of Eimeria species.

Action suppress the development of second generation schizonts.

- It causes stress problems when feed in hot whether and mode medicated birds more susceptible to heat stress.
- It is used as preventive against cocal and intestinal Coccidiosis in broiler 125 PPm in feed and also erplacment flocks up to 16 week of age.

Contraindication: Nicarbazin is not allowed to be given to laying hens and breeding hens as it reduces the egg production and hatchability and producing eggs with mottled (spotted) yolk, however it does not affect semen quality in males.

6- Guanidines.

* Robenidine

- Effective against intestinal and caecal Coccidiosis in poultry and rabbits.

Mechanism of action

It inhibits the oxidative phosphorylation of Emeria species and although its activity is primarily coccidiostate against the first generation of schizonts and some coccidiocidaleffect against second generation of schizonts and suppress oocyst production.

Action

Effective control of all turkey, chicken and intestinal coccidian of rabbits has been a chivied with continuous medication in feed control as preventive in chickens and turkeys.

Doses: 33 PPm in feed for broilers and Turkeys.

55-66 PPm in feed for rabbits.

Contraindication:

Robenidine should not be mixed with other Anticoccidials, and not in feed to laying hens.

A withdrawal period of 5 days is required before slaughtering.

Disadvantage: It taints the egg and meat.

7- Benzene Acetonitrile

Diclazuril

1- Diclazuril is brood spectrum anticoccidial and used for prophylactic medication in feed and recently introduced as oral solution for treatment.
2- Withdrawal period is zero.

Mechanism of Action

Its anticoccidial activity is species specific

- Acting against zygotes of E. maxima
- Acting against gametocytes of e. Brunette.
- Acting against schizont and gometcyte of E. acervuline E. tenella.

Precaution and warning:

The homogenous mixing of Diclazuril to the feed stuff is necessary to achieve full effect. The drug must be feed continuously to be fully effective, as birds in the field are picking up infections all the time.

Diclazuril is compatible with all therapeutics and feed additives, and produces such low tissue level that a zero-day withdrawal period is anticipated.

Doses; broilers, Turkeys and rabbits 1PPm in feed.

8- Symmetrical trizinones:

Toltrazuril

- Acts as coccidicidal for treatment of cecal and intestinal Coccidiosis.
- It is used in drinking water for treatment in chicken, rabbits and turkeys.
- Its acting is due to interfering with nuclear division of schizonts and prevent differentiation into micro and macro gametocytes

Does: 25PPm in water for 2 days.

Precaution and warning: Toltrazuril appears to be compatible with current in feed anticoccidials and antibiotics.

- It persists for very long time in tissues and a withdrawal period of 19 days is required.

9- Pyridine:

Clopidol

It is a synthetic anticoccidial agent and used for prevention of Coccidiosis in chickens and rabbits. Clopidol is broad spectrum anticoccidial agent being active against different Eimeria species as: *E tenella, E. necatrix, E. brunette, E. maxima, E. acervuline* and *E. praecox.*

A withdrawal period of 5 days is required before slaughtering.

Mechanism of action;

Clopidol prevents the development of the first generation schizonts, through its inhibiting action on the development of sporozoites and trophozoites in the 1 st asexual cycle.

Dosage

Broilers and replacement flock up to 16 week of age 125 PPm continuously.

Rabbits: 200 PPm in feed continuously.

Chickens and turkeys: 100 PPm clopidol + 8.35 Methylbenzoquate continuously (up to 12 weeks of age in turkeys).

Prevention & control of Coccidiosis

N.B Turkey are very sensitive to ionophores and Nicarbazine, these drugs are not used in turkey production

Prevention:

1- Avoid high humidity

2- Change the old litter

3- Provide good nursing during outbreaks.

Important programs for controlling of coccidian:

1- **Continues feeding, 3-5 days withdrawal.** Common program with one drug only used when Coccidiosis not cause a major problems.
2- **Continues feeding, 7-10 days withdrawal.** Mainly practiced when production period is more than 48 days.
3- **Shuttle program.** One drug used in the starter feed (2-3 weeks) and another in the grower feed.
4- **Rotation programs (Rolling program)** In this program, the same anticoccidial is used for several grow outs and then replaced by another.

Causes of Anticoccidial failure:

1- Application of not highly effective coccidiostates or development of resistance to particular coccidiostate.

2- Un-even distribution of coccidiostate in the feed.

3- Reduced feed intake for any cause (so bird not take preventive dose).

4- Incomplete mixing of anticoccidial drug.

5- Massive infection with virulent strains of Eimeria.

6- Management errors as *insufficient feeder & feeders to high inadequate water suppliers % inadequate litter management.*

Table (44): Anticoccidials used for treating broiler chickens.

Drug	*Year launched (approx)*	*Class*	*Food/water inclusion level (PPm)*	*Drug resistance*
Sulphaquinoxaline	1984	Sulphonamide	125	+
Nicarbazin	1955	Carbanilide	125	+
Amprolium	1960	Thiamine antagonist	125-150	+
Dinitrolmide	1960	Nitrobenzamide	125	+
Clopidol	1968	Pyridone	125	+
Decoquinate	1969	Quinolone	20-40	+
Monensin	1971	Ionophore	100-120	-
Robenidine	1972	Guanidine	33	+
Halofuginone	1974	Quinazoline	3	±
Lasalocid	1976	Ionophore	90	-
Salinomycin	1977	Ionophore	60	-
Arprinocid	1978	Benzylpurine	60	+
Narasin	1979	Ionophore	70	
Maduramicin	1984	Ionophore	5	-
Toltrazuril	1987	Symmetrical triazinone	25	-
Diclazuril	1989	Benzene acetonitrile	1	-
Combination products Amprolium		Thiamine antagonist	125	+
+ ethopabate		*Substituted benzoic acid	8	+
Amprolium		Thiamine antagonist	100	+
+ ethpabate		Substituted benzoic acid	5	+
+sulphaquinoxaline		Sulphonamide	60	+
Clopidol		Pyridone	100	+
+ methylbenzoquate		Quinolone	8.35	+
Narsain		Ionopnore	50	-
+ nicarbazin		Carbanilide	50	-

* Not yet available in UK.

Table (45): UK trade names of anticoccidials

Anticoccidial	*Trade name (company)*	
Amporlium	Amprol	(MSD)
Amporlium + ethopabate	Amporlmix	(MSD)
Amporlium + ethopabate + Sulphaquinoxaline	Pancoxin	(MSD)
Arprinocid*	Arprocox*	(MSD)
Clopidol	Coyden	(DOW)
Clopidol + methylbenzoquate	Lerbek	(DOW)
Decoquinate	Deccox	(May and Baker)
Diclazuril	Clinacox	(Janssen)
Dinitolmide (zoalene)	Salcostat	(Salsbury Labs)
	DOT	(Roche)
Halofuginon:	Stenerol	(Hoechst)
Lasalocid	Avatec	(Roche)
Maduramicin	Cygro	(Cyanamid)
Methylbenzoquate	Statyl	(ICI)
Monensin	Elancoban	(Elanco)
Narasin	Monteban	(Elanco)
Nicarbazin	Nicrazin	(MSD)
Robenidine	Cycostat	(Cynamid)
Salinomycin	Sacox	(Hoechst)
Sulphaquinoxaline	Embazin	(May and Baker)
Toltrazuril*	Baycox*	(Bayer)

* Not currently and available in UK.

Table (46):

Ionophorous antibiotics

Name	Chemical name (Empirical formula) [Molecular weight]	Chemical structure
Lasalocid	6-[7*R*-[5*S*-Ethyl-5-(5*R*-ethyltetra-hydro-5-hydroxy-6 *S*-methyl-2*H*-pyran-2*R*-yl) tetrahydro-3*S*-methyl-2*S*-furanyl]-4*S*-hydroxy-3*R*,5*S*-dimethyl-6-oxonon-yl]-2-hydroxy-3-methylbenzoic acid ($C_{34}H_{54}O_8$) [590.80]	
Maduramicin	(3*R*,4*S*,5*S*,6*R*,7*S*,22*S*)-23,27-Didemethoxy-2,6,22-tridemethyl-11-*O*-demethyl-22-[(2,6-dideoxy-3,4-di-*O*-methyl-β-L-arabino-hexopyranosyl)oxy]-6-methyl-oxylonomycin A monoammonium salt ($C_{47}H_{83}NO_{17}$) [934.17]	
Monensin	2-[5-Ethyltetrahydro-5-[tetrahydro-3-methyl-5-[tetrahydro-6-hydroxy-6-(hydromethyl)-3,5-dimethyl-2*H* -pyran-2-yl]-2-furyl]-2-furyl]-9-hydroxy-β-methoxy-α, γ. 2,8-tetramethyl-1,6-dioxaspiro [4.5] decane-7-butyric acid ($C_{36}H_{62}O_{11}$) [670.90]	
Narasin	(αβ.2β.3α.5α,6α)-α-ethyl-6-[5-[5-(5α-ethyltetrahydro-5β-hydroxy-6α-methyl-2*H*-pyran-2β-yl)-3″α,4,4″,5,5″α,6″-hexahydro-3′β-hydroxy-3″β,5α,5″β-trimethylspiro] furan-2(3*H*),2′-[2*H*]pyran-6′(3′*H*),2″-[2*H*]pyran[6″α-yl]2α-hydroxy-1α,3β-dimethyl-4-oxoheptyl]-tetrahydro-3,5-dimethyl-2*H*-pyran-2-acetic acid ($C_{43}H_{72}O_{11}$) [765.05]	
Semduramicin	(2*R*,3*S*,4*S*,5*R*,6*S*)-tetrahydro-2,4-dihydroxy-6-[(1*R*)-1-[(2*S*,5*R*,7*S*,8*R*,9*S*)-9-hydroxy-2,8-dimethyl-2-[(2*R*,6*S*)-tetrahydro-5-methyl-5-[(2*R*,3*S*,5*R*)-tetrahydro-5[(2*S*,3*S*,5*R*,6*S*)-tetrahydro-6-hydroxy-3,5,6-trimethyl-2*H*-pyran-2-yl]-3-[[(2*S*,5*S*,6*R*)-tetrahydro-5-methoxy-6-methyl-2*H*-pyran-2-yl]oxy]-2-furyl]-2-furyl]-1,6-dioxaspirol [4.5]dec-7-yl]ethyl]-5-methoxy-3-methyl-2*H*-pyran-2-acetic acid ($C_{44}H_{77}O_{16}$) [748.47]	

Table (47):

Ionophorous antibiotics

Name	Chemical name (Empirical formula) [Molecular weight]	Chemical structure
Lasalocid	6-[7*R*-[5*S*-Ethyl-5-(5*R*-ethyltetra-hydro-5-hydroxy-6 *S*-methyl-2*H*-pyran-2*R*-yl) tetrahydro-3*S*-methyl-2*S*-furanyl]-4*S*-hydroxy-3*R*,5*S*-dimethyl-6-oxonon-yl]-2-hydroxy-3-methylbenzoic acid ($C_{34}H_{54}O_8$) [590.80]	
Maduramicin	(3*R*,4*S*,5*S*,6*R*,7*S*,22*S*)-23,27-Didemethoxy-2,6,22-tridemethyl-11-*O*-demethyl-22-[(2,6-dideoxy-3,4-di-*O*-methyl-β-L-arabino-hexopyranosyl)oxy]-6-methyl-oxylonomycin A monoammonium salt ($C_{47}H_{83}NO_{17}$) [934.17]	
Monensin	2-[5-Ethyltetrahydro-5-[tetrahydro-3-methyl-5-[tetrahydro-6-hydroxy-6-(hydromethyl)-3,5-dimethyl-2*H*-pyran-2-yl]-2-furyl]-2-furyl]-9-hydroxy-β-methoxy-α, γ, 2,8-tetramethyl-1,6-dioxaspiro [4.5] decane-7-butyric acid ($C_{36}H_{62}O_{11}$) [670.90]	
Narasin	(αβ,2β,3α,5α,6α)-α-ethyl-6-[5-[5-(5α-ethyltetrahydro-5β-hydroxy-6α-methyl-2*H*-pyran-2β-yl)-3″α,4,4″,5,5″α,6″-hexahydro-3′β-hydroxy-3″β,5α,5″β-trimethylspiro] furan-2(3*H*),2′-[2*H*]pyran-6′(3′*H*),2″-[2*H*]pyran]6″α-yl]2α-hydroxy-1α,3β-dimethyl-4-oxoheptyl]-tetrahydro-3,5-dimethyl-2*H*-pyran-2-acetic acid ($C_{43}H_{72}O_{11}$) [765.05]	
Semduramicin	(2*R*,3*S*,4*S*,5*R*,6*S*)-tetrahydro-2,4-dihydroxy-6-[(1*R*)-1-[(2*S*,5*R*,7*S*,8*R*,9*S*)--9-hydroxy-2,8-dimethyl-2-[(2*R*,6*S*)-tetrahydro-5-methyl-5-[(2*R*,3*S*,5*R*)-tetrahydro-5[(2*S*,3*S*,5*R*,6*S*)-tetrahydro-6-hydroxy-3,5,6-trimethyl-2*H*-pyran-2-yl]-3-[[(2*S*,5*S*,6*R*)-tetrahydro-5-methoxy-6-methyl-2*H*-pyran-2-yl]oxy]-2-furyl]-2-furyl]-1,6-dioxaspirol [4.5]dec-7-yl]ethyl]-5-methoxy-3-methyl-2*H*-pyran-2-acetic acid ($C_{45}H_{72}O_{16}$) [748.47]	

Table (48):

Sulfonamides

Name	Chemical name (Empirical formula) [Molecular weight]	Chemical structure
Sulfadiazine	4-amino-*N*-2-pyrimidinylbenzenesulfonamide ($C_{10}H_{10}N_4O_2S$) [250.28]	
Sulfadimethoxine	4-amino-*N*-(2,6-dimethoxy-4-pyrimidinyl)-benzenesulfonamide ($C_{12}H_{14}N_4O_4S$) [310.33]	
Sulfadoxine	4-amino-*N*-(5,6-dimethoxy-4-pyrimidinyl)-benzenesulfonamide ($C_{12}H_{14}N_4O_4S$) [310.34]	
Sulfaguanidine	4-amino-*N*-(aminoiminomethyl)-benzenesulfonamide ($C_7H_{10}N_4O_2S$) [214.24]	
Sulfamethazine	4-amino-*N*-(4,6-dimethyl-2-pyrimidinyl)-benzenesulfonamide ($C_{12}H_{14}N_4O_2S$) [278.32]	
Sulfamethoxazole	4-amino-*N*-(5-methyl-3-isoxazolyl)-benzenesulfonamide ($C_{10}H_{11}N_3O_3S$) [253.31]	
Sulfaquinoxaline	4-amino-*N*-2-quinoxalinyl-benzenesulfonamide ($C_{14}H_{12}N_4O_2S$) [300.33]	
Sulfanitran	4′-[(*p*-nitrophenyl)sulfamoyl]acetanilide ($C_{14}H_{13}N_3O_5S$) [335.34]	

Table (49):

Dihydrofolate reductase/thymidylate synthase inhibitors

Name	Chemical name (Empirical formula) [Molecular weight]	Chemical structure
Trimethoprim	2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine ($C_{14}H_{18}N_4O_3$) [290.32]	
Pyrimethamine	2,4-diamino-5-(*p*-chlorophenyl)-6-ethylpyrimidine ($C_{12}H_{13}ClN_4$) [248.71]	
Diaveridine	2,4-diamino-5-veratrylpyrimidine ($C_{13}H_{16}N_4O_2$) [260.29]	
Ormetoprim	2,4-diamino-5-(4,5-dimethoxy-2-methylbenzyl)-pyrimidine ($C_{13}H_{15}N_4O_2$) [259.17]	

Table (50):

Diamidine derivatives

Name	Chemical name (Empirical formula) [Molecular weight]	Chemical structure
Amicarbalide	3,3′-(Carbonyldiimino)*bis*-benzene-carboximidamide ($C_{15}H_{16}N_6O$) [296.34]	
Diminazene	*N*-acetylglycine compounded with 4,4′-(1-triazene-1,3-diyl) *bis*-(benzenecarboximidamide) ($C_{22}H_{29}N_9O_6$) [515.54]	
Imidocarb	3,3′-di-2-imidazolin-2-yl-carbanilide ($C_{19}H_{20}N_6O$) [348.41]	
Pentamidine	4,4′-[1,5-pentanediylbis(oxy)]*bis*-benzenecarboximidamide ($C_{19}H_{24}N_4O_2$) [340.43]	
Phenamidine	4,4′-oxybisbenzenecarboximidamide ($C_{14}H_{14}N_4O$) [254.29]	

XV.VII. Pharmacology of Insecticides

- **Definition & characteristics**
- **Classification**

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EXTERNAL ANTIPARASITICS (INSENCTICIDES)

Uses: to control mites, fleas, lice, ticks and flies in the animal house and on its food.

Toxicity: individual animal vary in response to the toxic effect of the insecticide.

- Age: young and senile animals are more susceptible for toxicity.
- Health conditions: hepatic and renal diseases aggravate the toxic response.
- Species: some species and particular breeds are more susceptible for toxicity of certain insecticide. Ex. horses develop urticaria from insecticides and cats are very susceptible for cholinergic stimulants.
- Stress like high temperature, high humidity and traveling may aggravate the toxicity.

Formulations:

- Dips: are used for the control of mites, ticks, lice, keds, and flies in sheep, cattle, goats, and horses.
- Spray and shampoo
- Pour-ons and spot-ons contain the pesticide chemicals at relatively high concentration and are formulated to either penetrate the skin and act systemically or spread over the skin surface and act by contact.

- Oil spray
- Feed additives
- Collars, tapes, bands and ear tags
- Dusts

Seasonality:

- Many ectoparasite infestations are seasonal and predictable and can be countered by prophylactic use of ectoparasiticides.
- For example, in temperate countries flies are seen predominantly from late spring to early autumn, tick populations increase in the spring and autumn, and lice and mites during the autumn and winter months.
- Treatments can therefore be targeted at anticipated times of peak activity as a means of limiting diseases and parasite populations.

Insecticides are classified into:

- Organophosphates
- Carbamates
- Chlorinated hydrocarbons
- Macrocyclic lactones (macrolides endectocides)
- Insect growth regulators
- Botanicals (plant origin)
- Other insecticides

Organophosphates (OP):

- Contact, lipid soluble, absorbed rapidly from external on skin application or oral application and rapidly excreted without residue withdrawal problems.
- **MOA** is by irreversible binding to the cholinesterase enzyme of both the parasite and the host.
- Members include: **diazinon, dichlorophos, trichlorfon, malathion** and **famphor**.
- **Toxicity**
  - Acute toxicity includes the nicotinic effect that are summarized in the word SLUD (salivation, lacrimation, urination and defecation) and other nervous symptoms: ataxia, fasciculation and conculsion.
    - Treatment includes decontinuation of the OP and administration of atropine sulphate as non specific antidote and 2-PAM (paralidoxime) as a specific antidote.
  - Chronic toxicity causes demyelination of the peripheral nerves leading to severe nerve damage and consequently paralysis.
- Limitation of usage: drug resistance and drug misusage.

Carbamates:

- Are closely related to organophosphates and are anticholinesterases.
- They are contact insecticides and reversibly block AChE without changing it.
- The 2 main carbamate compounds used are carbaryl and propoxur.

- Carbaryl has low mammalian toxicity but may be carcinogenic and is often combined with other active ingredients.
- Toxic effect of carbamates is less than that of OP.
- Toxicity treatment lines are the same as that of OP but without 2-PAM (?)

Chlorinated hydrocarbons (organochlorines):

It has 3 subgroups

- 1. Chlorinated ethanes (DDT and methoxychlore)
    - Their action is by increasing the intracellular sodium ions and calcium ions influx increases in an attempt to exchange sodium with calcium leading to insect paralysis.
- 2. Cyclodeins (chlordane, dieldrin and heptachlor)
- 3. Hexachlorocyclohexanes (benzene hexachloride)
- The mode of action of the last 2 groups is by inhibiting GABA receptors in the insects.
- Organochlorines were used extensively as dips for ectoparasites for sheep, cattle and dogs and for house insects but are replaced by the organophosphates and pyrithrins due to resistance of the insects against them and the environmental concern.
- The environmental concern: is that they stay in the soil, buildings, animal tissues and almost every things for very long periods that may extend up to 20 years. Due to their residue in the environment they stay in the food chain and cause thinning of the egg shell and accumulation in the fish.
- Toxicity symptoms are expressed in ataxia, tremors, convulsion and tachypenea.

- Treatment of toxicity is by non specific therapy (symptomatic).

Macrocyclic lactones:

- Include ivermectin, abamectin, eprinomectin, doramectin, silamectin, milbimycin and moxidictin.
- The application of this group could be by oral, sc or pour on according to the targeted parasite.
- See for details on this group in the antinematodal section.

Insect growth regulators (juvenile hormone analogs):

- Includes **cyromazine, fenoxycarb and methoprene**
- MOA is by mimicking the action of the juvenile hormone keeping the larvae in the immature stage for ever without letting the reproductive organs to differentiate.
- Used therapeutically at the form of collars to control fleas in dogs and orally to control fecal magets in poultry.
- Their effect stays for 21 weeks.
- They can be mixed with pyrithrins to control the immature and mature insects.
- They are save as long as they are used according to the directions.

Botanicals:

- Are the drugs that are extracted from the plant.
- You can plant the plant itself around your yard and their odor comes from the plant and repel the flying insents.
- **Rotenone:**
    - Extracted form the derris plant.

- It is a stomach poison when absorbed it inhibits the cellular respiration and leading to reduction of the nerve conduction of the insect.
- Used successfully to control lice, fleas, mites and ticks and to kill unwanted fish in ponds and lakes with short time of persistence.
- Although safe they may cause CNS excitement, convulsion and depression in animals.

- **Pyrethrins (natural from chamomile flowers) and Pyrethoids (synthetic)**
  - They are used mainly as insect repellents.
  - Pyrethins get broken down by sunlight but pyrethroids not.
  - Pyrethoids may be used in the form of shampoo or lotions for lice and mites in pet animals.
  - MOA is by blocking nicotine receptors and stimulating GBA receptors.
  - Safe, but may cause allergy, nausea, vomiting and headach.
  - Treatment of adverse effects is symptomatically.

Other insecticides:

- **Sulpher:** the organic sulpher (tetmosole®) is used as emulsion or solution for mange in dogs, cats and cattle and the inorganic sulpher sublime is used as dips and ointment for sarcoptic, chorioptic and demodectic mange in animals.
  - MOA is by **suffocation** of the insect.
- **Amitraz:** is a formamidine compound

- MOA is by inhibiting the **MAO enzyme** in the insect leading to accumulation of the adrenergic transmitter. Also it stimulate the **octopamine receptors** in the insects.
- It is mainly acaricide for dogs, cats, cattle, pig but not for **horse**
- Needs zero withdrawal time in cattle but at leas 3 days for swine.
- Never used in horses as it cause severe colon impaction.

- **Lufenuron:**
  - Inhibits the chitin synthesis (chitin is needed for the egg shell formation and skeleton in flea larvae).
  - After its absorption it distributes to the adipose tissue and redispose to the blood reach the therapeutic level in 6-12 hours and stay in a therapeutic level for 32 days.
  - Used in dogs and cats older than 6 months to control fleas.
  - Has no effect against the adult fleas so it is mixed with pyrethoids in collars to give complete protection from fleas.

Table (51, 52):

Botanical compounds

Name	Chemical name (Empirical formula) [Molecular weight]	Chemical structure
Limonene	1-methyl-4-(1-methylethenyl)cyclohexene ($C_{10}H_{16}$) [136.23]	
Pyrethrins	Mixture of active constituents: pyrethrins I and II; cinerins I and II; jasmolins I and II	
Rotenone	[2*R*-(2α,6aα,12aα)]-1,2,12,12a-tetrahydro-8,9 -dimethoxy-2-(1-methylethenyl)-[1]-benzopyrano-[3, 4-b]furo[2,3-h][1]benzopyran-6(6a*H*)-one ($C_{23}H_{22}O_6$) [394.41]	

Synthetic pyrethroid compounds

Name	Chemical name (Empirical formula) [Molecular weight]	Chemical structure
Allethrin	2.2-dimethyl-3-(2-methyl-1-propenyl)cyclo-propanecarboxylic acid 2-methyl-4-oxo-3-(2-propenyl)-2-cyclopentenl-1-yl ester ($C_{19}H_{26}O_3$) [302.40]	
Cyfluthrin	3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-carboxylic acid cyanol(4-fluoro-3-phenoxyphenyl)-methyl ester ($C_{22}H_{18}Cl_2FNO_3$) [434.29]	
Cyhalothrin	3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl-cyclopropanecarboxylic acid cyano(3-phenoxy-phenyl)methyl ester ($C_{23}H_{19}ClF_3NO_3$) [449.86]	
Cypermethrin	3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-carboxylic acid cyano(3-phenoxyphenyl)-methyl ester ($C_{22}H_{19}Cl_2NO_3$) [416.30]	
Fenvalerate	4-chloro-α-(1-methylethyl)benzeneacetic acid cyano(3-phenoxyphenyl)methyl ester ($C_{25}H_{22}ClNO_3$) [419.92]	
Permethrin	3-(2,2-dichloroethenyl)-2.2-dimethyl-cyclopropane-carboxylic acid (3-phenoxyphenyl)methyl ester ($C_{21}H_{20}Cl_2O_3$) [391.29]	
Resmethrin	[5-(phenylmethyl)-3-furanyl]methyl 2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylate ($C_{[illegible]}H_{26}O_3$) [338.40]	

Table (53):

Chlorinated hydrocarbon compounds

Name	Chemical name (Empirical formula) [Molecular weight]	Chemical structure
Lindane	1α,2α,3β,4α,5α,6β-hexachlorocyclohexane ($C_6H_6Cl_6$) [290.85]	
Methoxychlor	1,1'-(2,2,2-trichloroethylidene) *bis*[4-methoxylbenzene] ($C_{16}H_{15}Cl_3O_2$) [345.65]	

Table (54):

Organophosphate compounds

Name	Chemical name (Empirical formula) [Molecular weight]	Chemical structure
Chlorfenvinphos	phosphoric acid 2-chloro-1-(2,4-dichlorophenyl)-ethenyl diethyl ester ($C_{12}H_{14}Cl_3O_4P$) [359.56]	
Chlorpyrifos	phosphorothioic acid O,O-diethyl O-(3,5,6-trichloro-2-pyridinyl) ester ($C_9H_{11}Cl_3NO_3PS$) [350.57]	
Coumaphos	phosphorothioic acid O-(3-chloro-4-methyl-2-oxo-2*H*-1-benopyran-7-yl) O,O-diethyl ester ($C_{14}H_{16}ClO_5PS$) [362.78]	
Diazinon	phosphorothioic acid O,O-diethyl O-[6-methyl-2-(1-methylethyl)-4-pyrimidinyl] ester ($C_{12}H_{21}N_2O_3PS$) [304.36]	
Dichlorvos	phosphoric acid 2,2-dichloroethenyl dimethyl ester ($C_4H_7Cl_2O_4P$) [220.98]	
Ethion	O,O,O,O-tetraethyl S,S-methylene bisphosphorodithioate ($C_9H_{22}O_4P_2S_4$) [384.48]	
Famphur	phosphorothioic acid O-[4-[(dimethyl-amino)-sulfonyl] phenyl] O,O-dimethyl ester ($C_{10}H_{16}NO_5PS_2$) [325.36]	
Fenthion	phosphorothioic acid O,O-dimethyl O-[3-methyl-4-(methylthio)phenyl] ester ($C_{10}H_{15}O_3PS_2$) [278.34]	
Malathion	[(dimethoxy phosphinothioyl)thio] butanedioic acid diethyl ester ($C_{10}H_{19}O_6PS_2$) [330.36]	

(continued)

Table (54, continued):

(continued)

Name	Chemical name (Empirical formula) [Molecular weight]	Chemical structure
Phosmet	phosphorodithioic acid S-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl] O,O-dimethyl ester ($C_{11}H_{12}NO_4PS_2$) [317.32]	O, O, S, N—CH_2—S—P—OCH_3, OCH_3
Primiphos	O-[2-(diethylamino)-6-methyl-4-pyrimidinyl]phosphorothioic acid O,O-dimethyl ester ($C_{11}H_{20}N_3O_3PS$) [277.28]	N, N, N, S, O, P, O, O
Tetrachlorvinphos	phosphoric acid 2-chloro-1-(2,4,5-trichlorophenyl)-ethenyl dimethyl ester ($C_{10}H_9Cl_4O_4P$) [365.95]	$(CH_3O)_2P$—O—C, O, ClCH, Cl, Cl, Cl
Trichlorfon	(2,2,2-trichloro-1-hydroxyethyl)-phosphonic acid dimethyl ester ($C_4H_8Cl_3O_4P$) [257.48]	Cl_3CCH—P—OCH_3, O, OH, OCH_3

Table (55)

Carbamate compounds

Name	Chemical name (Empirical formula) [Molecular weight]	Chemical structure
Carbaryl	1-naphthalenol methylcarbamate ($C_{12}H_{11}NO_2$) [201.22]	O—C—$NHCH_3$, O
Propoxur	2-(1-methylethoxy)phenol methylcarbamate ($C_{11}H_{15}NO_3$) [209.24]	O—C—$NHCH_3$, O, $OCH(CH_3)_2$

Table (56)

Miscellaneous compounds

Name	Chemical name (Empirical formula) [Molecular weight]	Chemical structure
Lufenuron (IDI)	*N*-[2,5-dichloro-4-(1,1,2,3,3,3-hexafluoropropoxy)-phenylaminocarbonyl]-2,6-difluorobenzamide ($C_{17}H_8Cl_2F_8N_2O_3$) [511.15]	
Diflubenzuron (IDI)	*N*-[[(4-chlorophenyl)amino]carbonyl]-2,6-difluoro-benzamide ($C_{14}H_9ClF_2N_2O_2$) [310.68]	
Ivermectin	22,23-dihydroavermectin B_1 ($C_{48}H_{74}O_{14}$) [875.10]	$R=C_2H_5$ B_{1a} $R=CH_3$ B_{1b}
Milbemycin oxime	5-didehydromilbemycin (oxime derivative) 80% A_4, 20% A_3 ($C_{31}H_{43}NO_7$) A_3 [541.68] ($C_{32}H_{45}NO_7$) A_4 [555.71]	R: CH_3 A_3 oxime C_2H_5 A_4 oxime
Pyriproxifen (IGR)	2-[1-methyl-2-(4-phenoxyphenoxy)ethox]pyridine ($C_{20}H_{19}NO_3$) [321.37]	
Fipronil	5-amino-1-[2,6-dichloro-4-(trifluoro-methyl)phenyl]-4-[(trifluoromethyl)sulfinyl]-1*H*-pyrazole-3-carbonitrile ($C_{12}H_4Cl_2F_6N_4OS$) [437.15]	
Imidacloprid	1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro-*N*-nitro-1*H*-imidazol-2-amine ($C_9H_{10}ClN_5O_2$) [255.66]	

(continued)

Table (56, continued)

(continued)

Name	Chemical name (Empirical formula) [Molecular weight]	Chemical structure
Methoprene (IGR)	11-methoxy-3,7,11-trimethyl-2,4-dodecadienoic acid 1-methylethyl ester ($C_{19}H_{34}O_3$) [310.48]	
Cyromazine (IGR)	*N*-cyclopropyl-1,3,5-triazine-2,4,6-triamine ($C_6H_{10}N_6$) [166.18]	
Doramectin	25-cyclohexyl-5-*O*-demethyl-25-de-(1-methylpropyl) avermectin A_{1a} ($C_{50}H_{74}O_{14}$) [899.13]	
Eprinomectin	(4″R)-4″-epi-(acetylamino)-4″-deoxyavermectin B_1 Component B1a, ($C_{50}H_{75}NO_{14}$) Component B1b, ($C_{49}H_{73}NO_{14}$)	component B_{1a}: R = C_2H_5 component B_{1b}: R = CH_3
Moxidectin	[6*R*,23*E*,25*S*(E)]-5-*O*-demethyl-28-deoxy-25-(1,3-dimethyl-1-butenyl)-6,28-epoxy-23-(methoxyimino) milbemycin B ($C_{37}H_{53}NO_8$) [639.83]	
Selamectin	(5*Z*,25*S*)-25-cyclohexyl-4′-*O*-de(2,6-dideoxy-3-*O*-methyl-*α*-L-*arabino*-hexopyranosyl)-5-demethoxy-25-de(2-methylpropyl)-22,23-dihydro-5-hydroxyiminoavermectin A_{1a} ($C_{43}H_{63}NO_{11}$) [770.00]	
Benzyl benzoate	benzoic acid phenylmethyl ester ($C_{14}H_{12}O_2$) [212.24]	

Table (57)

Ectoparasiticides for use on dogs and cats

Compound(s)	Marketed formulation(s)	Target animal(s)	Target parasite(s)
d-trans Allethrin (some formulations contain PBO[a], MGK 264[b] or sumethrin)	Shampoo	Dog, cat	Fleas, ticks
Amitraz	Dip	Dog	Mites
	Collar	Dog	Ticks
Benzyl benzoate	Lotion	Dog	Mites
Carbaryl (some formulations contain methoxychlor, PBO, BPG[c], MGK 326[d], and/or pyrethrins)	Shampoo	Dog, cat	Fleas, ticks, mites (some products claim efficacy against lice; see specific product labels)
	Spray	Dog, cat	
	Dust	Dog and/or cat	
	Ear drops	Dog, cat	
Chlorpyrifos (some formulations contain methoprene PBO, pyrethrins, or MGK 264)	Spray	Dog	Fleas, ticks
	Dip	Dog	Fleas, ticks, mites
	Collar		Fleas, ticks, mites
	Shampoo	Dog or cat	Fleas, ticks, mites
	Streaker (for back and chest streak treatment)	Dog	Fleas
Diazinon	Collar	Dog or cat	Fleas, ticks
Dichlorvos	Collar	Dog or cat	Fleas, ticks
Fipronil	Liquid (spot-on)	Dog, cat	Fleas, ticks
	Spray	Dog, cat	Fleas, ticks
Imidacloprid	Liquid (spot-on)	Dog, cat	Fleas
d-Limonene (some formulations contain linalool)	Spray	Dog, cat	Fleas
	Shampoo	Dog, cat	Fleas
	Dip (also may be added to shampoo)	Dog, cat	Fleas
Linalool (some formulations contain *d*-limonene)	Spray	Dog, cat	Fleas
Lindane	Dip, spray, bath	Dog	Fleas, ticks, lice, mites
Lufenuron (also combined with milbemycin oxime for dogs)	Tablet	Dog, cat	Fleas
	Six-month injectable	Cat	Fleas
Malathion	Liquid	Dog, cat	Fleas, ticks, lice
Methoprene (some formulations contain permethrin, chlorpyrifos or tetrachlorvinphos	Collar	Dog or cat	Fleas, ticks
	Liquid (spot-on)	Dog	Fleas, ticks
Methoxychlor (some formulations contain carbaryl)	Powder	Dog, cat	Fleas, ticks
	Collar	Dog	Fleas, ticks
Permethrin (some formulations contain PBO, MGK 264, MGK 326[b], pyrethrins, pyriproxyfen or BPG)	Collar, spray, shampoo, dip, cream rinse or topical concentrate (spot-on)	Dog and/or cat (see specific product labels)	Fleas, ticks (see specific product labels)
Phosmet	Dip	Dog	Fleas, ticks, mites
Propoxur	Collar	Dog	Fleas, ticks
Pyrethrins (some formulations contain PBO, MGK 264, MGK 326, BPG, permethrin, carbaryl, or rotenone)	Spray, foam, dust, shampoo, dip, or ear drops	Dog and/or cat (see specific product labels)	Fleas, ticks, or mites (some products claim efficacy against lice; see specific product labels)
Pyriproxyfen (combined with permethrin in certain formulations)	Spray, collar, liquid (spot-on), strip-on	Dog or cat	Fleas (combinations may control additional ectoparasites)
Resmethrin	Shampoo	Dog, cat	Fleas, ticks
Rotenone (some formulations contain pyrethrins)	Ear drops	Dog, cat	Mites
	Dip	Dog	Fleas, ticks, lice
Selamectin	Liquid (spot-on)	Dog	Fleas, ticks, mites
		Cat	Fleas, mites

[a]PBO = piperonyl butoxide (synergist).
[b]MGK 264 = *N*-octyl bicycloheptene dicarboximide (synergist).
[c]BPG = butoxypolypropylene glycol (repellent).
[d]MGK 326 = di-*n*-propyl isocinchomeronate (repellent).

Table (57, continued)

Extoparasiticides for use on cattle

Compound(s)	Marketed formulation(s)	Method of application	Target parasite(s)
Amitraz	Liquid	Spray	Lice, ticks, mites
Chlorpyrifos	Liquid	Spray	Screwworm, ear ticks
Chlorpyrifos, diazinon	Ear tag	One tag in each ear	Horn flies, face flies, stable flies, house flies, lice, ticks
Coumaphos	Wettable powder	Spray or dip	Horn flies, lice, ticks, grubs, screwworms, mites
	Liquid	Spray or dip	Horn flies, lice, mites, ticks, grubs
	Dust	Dust bag or shaker can	Horn flies, face flies, ticks
Cyfluthrin	Ear tag	One tag in each ear	Horn flies, face flies, Gulf Coast ticks, ear ticks
Λ Cyhalothrin	Ear tag	One tag in each ear	Horn flies, face flies
	Pour-on	Backline treatment	Horn flies, lice
Cypermethrin, chlorpyrifos	Ear tag	One tag in each ear	Horn flies, face flies, Gulf Coast ticks, ear ticks
Beta-cypermethrin (zetamethrin)	Ear tag	One tag in each ear	Horn flies, face flies, ticks, lice
Diazinon, chlorpyrifos	Ear tag	One tag in each ear	Horn flies, face flies, stable flies, houseflies, lice, ticks
Dichlorvos (some formulations contain pyrethrins)	Liquid	Spray	Stable flies, horn flies, houseflies, mosquitoes, gnats
Diflubenzuron	Bolus	1 bolus per 1,100 lb	Horn flies, face flies, houseflies, stable flies
Doramectin	Injectable solution	Inject subcutaneously	Grubs, mites, biting and sucking lice
	Pour-on	Backline treatment	
Eprinomectin	Pour-on	Backline treatment	Grubs, mites, biting and sucking lice, horn flies
Ethion	Ear tag	One tag in each ear	Horn flies, face flies, stable flies, lice, ticks
Famphur	Pour-on	Backline treatment	Grubs, lice
	Liquid	Spray, spot-on, backrubber	Horn flies, lice, mites, ticks (spectrum depends on formulation)
Fenthion	Pour-on	Backline treatment	Lice, horn flies
	Ear tag	One tag in each ear	Horn flies, face flies
	Low-volume pour-on	Spot treatment on the backline	Grubs, lice
	Pour-on	Backline treatment	Grubs, lice
Fenvalerate	Ear tag	One tag in each ear	Horn flies, face flies, stable flies, houseflies, ticks, lice
Invermectin	Injectable solution	Inject subcutaneously	Grubs, mites, sucking lice
	Pour-on	Backline treatment	Grubs, mites, biting and sucking lice, horn flies
	Sustained-release bolus	Oral	Grubs, sucking lice, mites, ticks
Lindane	Spray	Direct application to infested site	Ear ticks, screwworms
Malathion	Liquid	Spray, backrubber	Horn flies, lice, ticks
Moxidectin	Pour-on	Backline treatment	Grubs, mites, biting and sucking lice, horn flies
Permethrin	Liquid	Spray	Horn flies, face flies, mites, ticks, lice, various other flies
	Liquid	Spray	Horn flies, face flies, stable flies, horseflies, lice, ticks, mites
	Wettable powder	Spray	Horn flies, face flies, stable flies, horse flies, lice, ticks, mites
	Dust	Direct application	Horn flies, face flies, lice
	Ear tag	One or two tags	Horn flies, face flies (generally two tags), Gulf Coast ticks, ear ticks (some tags do not claim horn flies)
	Roll-on paste	Roll on to different body areas	Horn flies, face flies, stable flies, black flies, houseflies, botflies

Table (57, continued)

(continued)

Compound(s)	Marketed formulation(s)	Method of application	Target parasite(s)
Permethrin, chlorpyrifos	Ear tag	One or two tags	Horn flies, face flies (generally two tags), Gulf Coast ticks, ear ticks
Permethrin	Pour-on	Backline treatment	Horn flies, face flies, lice
Pirimiphos	Ear tag	One tag in each ear	Horn flies, face flies
Tetrachlorvinphos	Premix	Mix in feed	Horn flies, face flies, houseflies, stable flies
	Wettable powder	Spray	Horn flies, lice, ticks
	Dust	Dust bag, shaker can	Horn flies, lice, face flies
Trichlorfon	Dust	Dust bag	Horn flies, face flies, ticks
	Wettable powder	Spray	Horn flies, lice, ticks

Note: Some products also may contain synergists and/or repellents.
Refer to label directions for compounds approved for lactating dairy cattle and for compound withdrawal period prior to slaughter

Ectoparasiticides for use on sheep and goats

Compound(s)	Marketed formulation(s)	Method of application	Target parasite(s)
Fenvalerate	Liquid	Spray, pour-on	Lice, keds
Ivermectin	Drench (sheep only)	Oral drench	Nasal bots
Lindane	Spray	Direct application	Ear ticks, screwworms
Malathion	Emulsifiable concentrate	Spray	Lice, keds, ticks
Permethrin	Liquid	Spray	Lice, ticks (some formulations also claim activity against keds or various flies)
	Pour-on	Pour-on	Lice, keds
	Emulsifiable concentrate	Spray	Lice, ticks, blowflies

Note: Refer to label directions for compounds approved for lactating goats and for compound withdrawal period prior to slaughter.

Ectoparasiticides for use on swine

Compound(s)	Marketed formulation(s)	Method of application	Target parasite(s)
Amitraz	Liquid	Ears and backline treatment	Lice, mites
Coumaphos	Dust	Shaker can	Lice
	Liquid	Spray	Lice
Doramectin	1% injectable solution	Inject subcutaneously	Lice, mites
Fenthion	Pour-on	Pour-on	Lice
Fenvalerate	Liquid	Spray, pour-on	Lice, mites (pour-on only for lice)
Ivermectin	1% injectable solution	Inject subcutaneously	Lice, mites
	0.27% injectable solution	Inject subcutaneously	Lice, mites
	Pre-mix	Mix with feed	Lice, mites
Lindane	Spray	Direct application	Ear ticks, screwworms
Malathion	Liquid	Spray	Lice, mites
Permethrin	Liquid	Spray, paint, dip	Lice, mites (some formulations also claim horn flies, and ticks
	Dust	Direct application	Lice (some formulations also claim horn flies, ticks, and mites)
	Wettable powder	Spray, paint, dip	Horn flies, lice, ticks, mites
Tetrachlorvinphos	Wettable powder	Spray	Lice
	Dust	Direct application	Lice

Note: Refer to label directions for compound withdrawal period prior to slaughter.

Table (57, continued & 58)

Ectoparasiticides for use on horses

Compound(s)	Marketed formulation(s)	Method of application	Target parasite(s)
Coumaphos	Liquid	Spray	Horseflies, ticks, screwworms, lice
	Emulsifiable concentrate	Spray	Horseflies, ticks, screwworms, lice
Fenvalerate	Liquid	Spray	Horn flies, face flies, stable flies, houseflies
Ivermectin	Paste	Oral	Botfly larvae
	Liquid	Oral	Botfly larvae
Lindane	Spray	Direct application	Ear ticks, screwworms
Malathion	Liquid	Spray	Horn flies, lice, ticks
Methoxychlor, pyrethrins	Liquid	Spray, wipe	Horn flies, horseflies, stable flies, deerflies
Moxidectin	Gel	Oral	Botfly larvae
Permethrin (some formulations also contain pyrethrins)	Liquid	Spray, wipe	Horn flies, face flies, horseflies, stable flies, deerflies, mosquitoes, biting gnats, ticks
	Dust	Direct application	
Pyrethrins	Liquid	Spray	Horn flies, face flies, houseflies, horseflies, stable flies, deerflies, mosquitoes, biting gnats, ticks

Benefit-risk ratios of selected classes of ectoparasiticides

Class of ectoparasiticide	Mammalian toxicity (mg/kg)	Insect toxicity (mg/kg)	Benefit-risk ratio[a]
Carbamates	45	2.8	16
Organophosphates	67	2.0	33
Chlorinated hydrocarbons	230	2.6	91
Synthetic pyrethroids	2000	0.45	4500

Source: MacDonald and Miller 1986.
[a]Safety factor in mammals (usually oral LD$_{50}$ in rat) ÷ toxicity to insect (usually contact LD$_{50}$ in flies).

Table (59):

Clinical signs and treatment of ectoparasiticide toxicosis

Ectoparasiticide group	Clinical signs of toxicosis	Treatment
Carbamates	Abdominal cramping, vomiting, diarrhea, miosis, dyspnea, cyanosis, muscle twitching seizures; rarely tetany followed by weakness and paralysis	Atropine sulfate: 0.2–0.5 mg/kg to effect (mydriasis and reduced salivation) usually 1/4 dose IV and 3/4 SC; may need to repeat at 3–6 hr for 1–2 days depending on response; 2–PAM (pralidoxime) is contraindicated
Chlorinated hydrocarbons	Onset can be minutes to days after exposure, usually several hours; signs include apprehension, exaggerated response to stimuli, vomiting, muscle twitching of face and head that progresses posteriorly to severe fasciculations and tremors; clonic and tonic seizures; elevated body temperature; chlorinated hydrocarbons are stored in fat; therefore, course may be protracted	Emesis (may induce seizures), gastric lavage; no specific antidote; seizures may be controlled with diazepam at 2.5–20 mg IV as needed; barbituate to effect; do *not* use phenothiazines, because they lower seizure threshold; calcium gluconate 10% at 2–10 mL given slowly IV and vitamin B complex IM to protect liver function; critical period, 24–36 hr
d-limonene, linalool, crude citrus oil extracts	(Cats) Hypersalivation, ataxia, and muscle tremors; hypothermia in some animals	Supportive therapy; wash agent from hair coat with nondetergent-, nonalcohol-containing shampoo; external warming for hypothermia
Formamidines	Lethargy, hypotension, hyperglycemia, mydriasis, hypothermia, bradycardia, ataxia, vomiting, and diarrhea have also been reported	Emesis, activated charcoal after oral ingestion (collar); wash agent from hair coat with nondetergent-, nonalcohol-containing shampoo (dip); yohimbine 0.1 mg/kg IV
Organophosphates	*Muscarinic:* salivation, lacrimation, diarrhea, abdominal cramping, miosis, pallor, cyanosis, dyspnea, emesis	Atropine as for carbamates
	Nicotinic: twitching of facial and tongue muscles progressing to generalized twitching followed by paralysis	2-PAM (pralidoxime): 20 mg/kg IV twice per day; give over 5-min duration; if poisoned for less than 24 hr, treatment is necessary for 1–2 days; if longer, therapy may be required for several days
	Central nervous system: depression, tonic/clonic seizures, death is due to hypoxia from respiratory muscle paralysis, bronchoconstriction, excessive pulmonary secretions, pulmonary edema, and bradycardia	Diphenhydramine hydrochloride: animal becomes depressed, decrease 4 mg/kg IV (dogs) or IM (dogs or cats) every 8 hr until asymptomatic; if animal becomes depressed, decrease dose to 1–mg/kg
Pyrethrins, synthetic pyrethroids	Only at very high doses; hypersalivation, vomiting, diarrhea, ataxia, CNS excitation and seizures, hyperthermia, hypothermia	Supportive as for chlorinated hydrocarbons; wash agent from hair coat with nondetergent-, nonalcohol-containing shampoo, monitor and control body temperature
Rotenone	Vomiting, nausea, diarrhea, respiratory stimulation, convulsions, followed by respiratory depression, coma, respiratory failure and death; in humans, causes irritant dermatitis	Emesis, gastric lavage before convulsive state; warmth, quiet; assist respiration; diazepam, calcium gluconate and B complex vitamins as for chlorinated hydrocarbons

Source: Modified from Kwochka 1987.

XV.VIII. ANTISEPTICS AND DISINFECTANTS

- **Definitions and Classification**
- **Phenol & phenol derivatives**
- **Oxidizing agents**
- **Reducing agents**
- **Alcohols**
- **Acids & Alkalis**
- **Dyes**
- **Surfactants**
- **Salts of heavy metals**
- **Halogens**

BY: ABUBAKR M. EL-MAHMOUDY, PhD

Antiseptics

Are chemical agents applied to living tissues (tissues & mucous membranes) to kill or inhibit the growth of micro-organisms. They are mostly static at the recommended concentrations.

Disinfictants

Are chemical agents applied to non-living surfaces to destroy micro-organisms (except spores). They are mostly cidal at the recommended concentrations.

Both antiseptics and disinfectants affect micro-organisms within few minutes unlike antibiotics which affect them after several hours from exposure.

Characters of good antiseptics/disinfectants

An ideal antiseptic/disinfectant should:

- be effective at small concentration.
- be effective in presence of organic matter.

- have rapid and sustained action.
- have a broad spectrum activity.
- be safe to skin and mucous membranes
- be safe and not corrosive to metals and other instruments.
- not stain surfaces and tissues to which it is applied.
- have pleasant odor.
- be soluble in water, stable and cheap

Evaluation of antiseptic/disinfectant efficiency

The effectiveness of an antiseptic/disinfectant is determined by what is called "Phenol coefficient" which is the concentration of the antiseptic/disinfectant that gives the same antiseptic/disinfectant action of 1% standard phenol solution. The comparison between the unknown antiseptic/disinfectant solution(s) and the standard phenol solution must be carried out exactly under the same experimental conditions of temperature, time, bacterial strain, bacterial cell number ...etc.

Classification

Antiseptics and disinfectants are classified according to their nature into:

A. Physical; including heat, light, filters, osmotic agents

B. Chemical; including chemical substances and solutions

A. Physical antiseptics/disinfectants

Physical antiseptics/disinfectants are classified according to their nature or mode of action into:-

A.1. Heat:

- Heat act by coagulation of bacterial proteins killing them.

- Various forms of heat could be used such as boiling, pasteurization, autoclaving or direct dry heat.

A.2. Light:

- Ultraviolet rays have antiseptic/disinfectant action by their cytotoxic action on bacterial cells.

A.3. Filters:

- They should have particular pore size that mechanically separates bacterial cells leaving a sterile liquid.
- examples are Zeits filter and Berkfield filter

A.4. Osmotic agents:

- Examples are hypertonic solutions of NaCl (10%) or glucose (10%).
- They act by withdrawing of intra-bacterial cell water leading to their dehydration.

B. Chemical antiseptics/disinfectants

Chemical antiseptics/disinfectants are classified according to their chemical nature into the following groups:

1- Phenol & phenol derivatives
2- Oxidizing agents
3- Reducing agents
4- Alcohols
5- Acids & Alkalis
6- Dyes
7- Surfactants
8- Salts of heavy metals
9- Halogens

B.1. Phenol & phenol derivatives

Actions:

- Phenol or carbolic acid is used as antiseptic at low concentration (0.5 %) because of its toxic potential.
- Higher concentrations are used as disinfectants.
- It is now of limited use but still considered as the "standard disinfectant" by which other disinfectants are judged by calculating their phenol coefficients.

Mode of action:

Precipitation of bacterial proteins

Phenol derivatives:

a. Cresol:

- It used as disinfectant at 2% aquous solution.

b. Cresote:

- It is colorless liquid composed of cresol and guaiacol.
- It is used as:
    - 5 ~ 10% ointments or oily solutions for ring worm in cattle.
    - Inhalation in respiratory affections & T.B.

c. Thymol:

- It is less toxic with bactericidal, fungicidal & parasiticidal actions.
- Uses:
    - Internally, as solution for hook worms
    - Ointment in skin affections
    - With other preparations as nasal drops and mouth washes
    - Preservation of urine samples for further analysis

d. Trinitrophenol (picric acid):

- Used in burns as:

- 1% aquous solution
- 1-3% alcoholic solution
- 1-3% ointment

e. Resercinol

- used externally as keratolytic to remove dandruff & scales in skin diseases as "ring worm" as alcoholic solution alone or with benzoic or salicylic acids.
- used also to remove warts & cornified skin
- 1-10% watery solution used as vagainal douche for its antipruritic effect.

f. Synthetic phenol derivatives as chlorhexidine & hexachlorophene

- These are non-irritant potent antiseptics even in presence of pus, serum or organic matters.
- Act in addition by disruption of cell wall of the microorganism.
- 0.5% alcoholic or 1% aquous antiseptic solution for skin.
- used also as pessaries in metritis

Toxicity of phenols:

- Penetrate tissues producing coagulative necrosis and ulcerations which is not painful at the beginning due to the local anesthetic effect of phenol.
- After absorption, they affect CNS leading to tremors, convulsions, respiratory failure & death

Treatment:

- Na or Mg sulfate to precipitate phenol as sulfate
- Stomach wash, avoid gastric intubation.
- Demulcents as milk or olive oil
- Anticonvulsants

B.2. Oxidizing agents

Mode of action:

They act by liberating nascent oxygen upon contact with organic matter.

Atomic oxygen then oxidizes the enzyme system of bacteria.

Members:

Oxidizing chemical antiseptics include:

a. H_2O_2:

- available concentrations are 10, 20, 30 %
- Uses:
    - mainly to clean old wounds, ulcers and septic sockets
    - mouth wash as gargles
    - enema for fecal impaction

b. Na perborate

- it is used as 2% solution as mouth wash

c. Pot. Permanganate

- 1:1000 aquous solution to clean ulcers& absceses
- 1:4000 aquous solution as mouth wash & vagainal douch
- 1:10000 aquous solution as urethral irrigation
- 5% as syptic due to astringent action
- 0.2 % as oxidizing agents in alkaloidal poisoning

B.3. Reducing agents

Mode of action:

They act by reduction of bacterial proteins resulting in bactericidal effects.

Members:

a. Formaldehyde & Gluteraldehyde

- They used as such as fumigant gases;

- Or dissolved in water forming formaline solution 3.7% which is used as:
    - Disinfictant for walls & ceiling of farms
    - Preservative for histopathological samples

b. Sulfur dioxide

- Used as fumigant disinfectant in animal farms
- Solid boxes are burnt as 0.5 kg for 100 m2
- Can be dissolved in H_2O to form sulphurous acid which is bactericidal
- Animal farms should be kept closed after fumigation.

B.4. Alcohols

- They act by dehydrating bacterial cells
- Examples are ethyl alcohol or isopropyl alcohol 70%. Lower or higher concentrations are less effective
- They are used as antiseptics for skin before injections & surgical operations.

B.5. Acids & alkalies

Mode of action:

Acids and alkalies act by lowering or elevating PH of the medium with the result of inhibiting bacterial cell activity.

Examples:

- Mineral acids are of limited use because of their corrosive action.
- Organic acids as benzoic, salicylic or boric acids.
- Alkalies as NaOH and Na carbonate which is commonly used in FMD.

a. Benzoic acid:

- Bacteriostatic & fungistatic
- Used as food preservative at 0.1 % solution.

- Used as 6% ointment in ring worm

b. Salicylic acid:

- Antiseptic & keratolytic.
- Used in the form of dusting powder, ointments or lotions for treatment of parasitic skin diseases & removal of warts & scales (as resercinol)

c. Boric acid:

- Non-irritant.
- Used as 2-4% solution for mouth wash, eye lotion, vaginal douche & urethral irrigation.

B.6. Dyes

Def.: These are synthetic organic substances with characteristic colors and astringent and antiseptic effects.

Members:

a- Azodyes as scarletred & demazon:

- Used as dusting powders or 4-8 % ointment in burns, chronic ulcers.
- It has a stimulating action on proliferation of epithelial cells.

b- Acridine dyes as acriflavine, proflavine & rivanol:

- Used as1:1000 antiseptic solution for wounds, ulcers & abscesses.
- Used as 1: 5000 for bladder irrigation.

c- Fluorocein dyes as mercurochrome:

- It is a mercurial compound used as 2% solution.
- Used as antiseptic for wounds & mucous membranes.

d- Rosaniline dyes as crystal violet, methyl violet, gentian violet, brilliant green & carbolfuchsin:

- Used a 1:500- 1:1000 as antiseptic for infected skin wounds.

e- Methylne blue:

- Antiseptic, molecular oxygen carrier

- 1% solution used in treatment of trichomonas vagainalis

- Antidote for CO & cyanide poisoning, i.v.

B.7. Surfactants

Antiseptics used for general cleaning purposes & emulsification

Mode of action:

- They act by lowering surface tension of greesy dirts removing it with the adherent bacteria.

Examples:

a- Hard soap (NaOH + oil) used as cleansing tool.

b- Soft soap (KOH + oil) used as emulsifying agent for external use

c- Cetrimide:

0.1 % for cleaning hands, clothes of milkers , udder & utilities in dairy farms.

B.8. Halogens

The antiseptic halogens include chlorine & iodine.

They act by denaturation of microbial proteins and by oxidizing sulphydryl groups of bacterial enzymes.

a- Chlorine:

- Gas with disinfectant & deodorant properties.
- It destroys bacterial toxins.
- It is used as water disinfectant at concentrations of 0.2- 0.4 ppm in the following forms:

  - Na hypochlorite (Clorox)® which releases chlorine slowly when exposed to atmosphere or organic matter.

  - Chlorinated lime (bleeching powder) which made by exposing lime to chlorine.

- Eupad: equal parts of chlorinated lime + boric acid
- Eusol: 2.5% eupad solution.

b- Iodine:

- Used as antiseptic in the following forms:
    - Diluted tincture 2.5 % in wound, ulcer & dressing before surgical operations
    - Strong tincture 5 % as counter irritant.
    - Iodine ointment 7-10% as antifungal for ring worm.
    - Lugol's iodine 0.5 % or less in endometritis
    - Iodophore (Povidone iodine; betadine®) releases iodine over long periods. It is a complex between PVP + iodine

B.9. Salts of heavy metals

They are astringent and antiseptic salts, including:

a- Mercury salts:

2- Mercuric chloride (corrosive sublimate): It has antiseptic effect but <u>not</u> used clinically for its high toxic potential

3- Mercurous chloride (calomel): It acts as antiseptic in the form of 2.5% ointment for treatment of hoof thrush & canker in equines. Internally acts as irritant purgative but not recommended

4- Oxides of mercury:

- They include yellow oxide, red oxide and black oxide.
- The commonly used is <u>yellow oxide of mercury 1%</u>. It is used as antiseptic & astringent for treatment of conjunctivitis, corneal ulceration & eczema of the eye lid.

4- Bin-iodide of mercury:

- It is antiseptic, astringent & counter irritant used as ointment for:
    - treatment of ring worm in cattle

- blister for sprain tendon & enlarged joints

5- Ammoniated mercury:

- It is used as 2.5% ointment for treatment of seborrhea, fissured heels & parasitic skin diseases.

6- Mercury:

- Externally, used as "blue ointment" in skin affections
- Internally, used as "blue pills or powder" as purgative
- Its use has been stopped for its cumulative & toxic effects

b- Copper:

- It is used as astringent & antiseptic as copper sulfate in the following forms:

  # 1:500 solution as astringent collyrium for treatment of granular conjunctivitis

  # 5-10% solution for treatment of ulcers of FMD in foot & mouth disease.

  # 5-10% solution or even powder for treatment of skin ulcers & fistulae.

  # In water reservoirs:

  - 1:1000,000 for preventing growth of algae
  - 5:1000,000 for destruction of snails which act as intermediate hosts for helminthes.

  # Internally: 0.3% solution should be given for ewes during pregnancy to avoid hypocopperemia & sway back disease.

c- Silver:

- It is astringent, antiseptic & styptic as silver nitrate salt.
- Used in the form of 1% solution in:
  - Treatment of keratoconjunctivitis.

- Cauterization of corneal ulcers & superficial wounds.
- It forms a layer of "silver proteinate" which protect underlying layers until healing
- It also releases silver ions which acts as antiseptic.

d- Lead:

- Astringent, antiseptic & styptic as "lead acetate"
- Used as lotions for soothing superficial inflammations, synovitis, traumas & sprain tendon.
- Usually used with zinc sulfate as "white lotion"

e- Zinc:

- It is astringent antiseptic including:

Soluble salts as: - zinc sulphate - zinc chloride	**Insoluble** salts as: - zinc oxide - zinc carbonate "Calamina"
. Irritant . Used as 0.25% with boric acid 2% or NaCl 0.9% as eye drops in conjunctivitis.	. Non irritant . Used as lotions or ointment for treatment of dermatitis

f- Aluminium:

- It has antiseptic, astringent & styptic actions
- It used in the form of alum or kaolin:

Alum (Aluminium sulphate + Amm. sulphate) or (Aluminium sulphate + Pot. sulphate)	**Kaolin** (aluminium silicate)
- 1~10% solutions of alum in H_2O or glycerine used in inflamed skin. - 1% aqueous solution used as vaginal douche in leukorrhea. - "Glycerinum alum" composed of 20 parts of Alum. Triturate + 7.5 parts of distilled water + 120 parts of glycerine And used for treatment of ulcerative stomatitis.	- Internally, used as intestinal astringent in various forms of diarrhea - Externally, used as cataplasma Kaolin used as heat poultice for unripe abscess

g- Bismuth:

- It has astringent, antiseptic & sedative effects.
- It used in the form of carbonate, subnitrite & silicate salts
- Uses:

Externally,

- Bismuth Carbonate powder in dermatitis
- Bismuth subnitrite paste in treatment of fistulae

Internally,

- Bismuth salt powder used for treatment of various forms of diarrhea by their astringent action

XVI. DRUG INTERACTIONS

- **Definitions**
- **Classification**
- **Drug-Drug interaction**
- **Drug-Food interaction**

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DRUG INTERACTIONS

What is drug interaction ?

An interaction is said to occur when the effects of one drug are changed by the presence of another drug, food, drink or by some environmental chemical agent.

The outcome of drug interaction may be: -

1. Harmful if interaction causes an :-

    a) Increase in efficacy or toxicity of the drug e.g.warfarin and phenylbutazone .

    b) Decrease in efficacy as an increase in the dosage of warfarin to maintain adequate anticoagulation if patient receive rifampicin .

2. Benificial e.g. antihypertensive drugs and diuretics for treatment of hypertension; sulphamethoxazole and trimelhoprim .

Classification of drug interactions:-

(A) According to clinical significance:

Drug — drug interactions are classified according to clinical significance into:

1. Major drug interactions:

It include interactions which are relatively well documented and potentially harmful to the patient .

2. Moderate drug interactions:

It include interactions for which more documentation is needed and /or the potential harm to the patient is less.

3. Minor drug interactions:

These include those interactions which may occur but which are least significant because of poor documentation, slight potential harm to patient and low incidence of interaction .

(B) According to type of interaction :

1. Pharmaceutical interactions .
2. Pharmacological interactions

1. Pharmaceutical interactions :-

These interactions may occur as follows:

1. 1. In intravenous fluid containers:-

This type may be physical or chemical as:

1.1.1. Precipitation reactions: as a result of changes in pH or concentrations e.g.

* Addition of digoxin, phenotoin, phenobarbitone to intravenously administered fluid induces precipitation.
* Addition of sodium bicarbonate to calcium gluconate solutions produces precipitate of calcium carbonate.

* Amphotercin B precipitates in electrolyte solutions, therefore it must be first disolved in 5% dextrose.

1.1.2. Loss of potency:-

When drug is added to large volume of infusion fluids e.g. penicillin in infusion that contain glucose or lactate.

1.2. Interactions in syringe:

These interactions are attributed to chemical changes:-

1.2.1. pH :

The stability of drugs in solution is pH dependent e.g.

- Alkaline solutions as those containing sulphonamides, aminophylline inactivate penicillin G and cephalosporins.
- Ampicillin and frusemide are inactivated in acidic media (Ringer's solution, solutions of B - complex vitamins).

1.2.2. Oxidation - reduction:

Tetracyclines are oxidized by riboflavin and phenothiazine is oxidized by ferric salts .

1.2.3. Complex formation: e.g. multivalent cations interacted with anionic drugs lead to formation of less soluble chelates e.g. cisplatin (anti cancer) should not be administered using aluminium needles because aluminium inactivates cisplatin .

1.3. Interactions within the dosage form:

This type occurs or results from interaction between various ingridients of the formulation e.g.

- Interactions between the various components of the suger coat which result upon storage. These interactions are accelerated in humid and hot storage condition.

2. Pharmacological interactions:-

2.1. Pharmacokinetic interactions: -

Pharmacokinetic interactions are those which affect absorption, distribution, biotransformation and excretion.

2.2.1. Drug absorption interactions:-

Drug affected	**Interacting drugs**	**Effect of interaction**
1. Effects of changes in G.I.T. pH : -		
a) Tetracyclines	Sodium bicarbonate	50% decrease in absorption.
b) Salicylates	Sodium bicarbonate	Slow absorption.
c) Quinolones	Sodium bicarbonate	Slow absorption
2. Adsorption, chelation and complexation		
a) Some drugs	Charcoal	Adsorption→decrease absorption.
b) Quinolones	Drugs containing Al^{3+}	Formation of poorly soluble chelates → reduce antibiotic absorption
3. Changes in G.I.T. motility :-		
a) Drugs orally administered	Purgatives	Decreased absorption
b) Drugs orally administered	Anticholinergic drugs	Increased absorption.

2.1.2. Drug distribution interactions:-

Many drugs (e.g. sulphonamides, salicytates, NSAIDs) are highly bound to plasma albumin. Displacement of bound drugs may occur when a second drug with greater binding affinity is administered concourrently. The resulting increase in free drug concentration may produce: a) increase the pharmacological activity that may lead to drug toxicity increase metabolism and excretion lead to shorten in the duration of action. b) increase metabolism and excretion lead to shorten in the duration of action

Drug affected	**Interacting drugs**	**Effect of interaction**
a) Warfarin	Phenylbutazone	Increase anticoagulant effect of warfarin.
b) Phenandion	Salicylates	Haemorrhage.
c) Sulphonamide	Coumarin	Increase antibacterial effect of sulphonamide.

2.1.3. Drug metabolism (biotransformation) interactions: -

This is usually the result of the action of interacting drug on the activity of liver microsomal enzymes. This alteration includes:-

2.1.3.1. Enzyme induction :

Drugs that induce hepatic microsomal enzymes include barbiturates (specially phenobarbital), phenylbutazone, rifampin, phenytoin and halogenated hydrocarbon insecticides. The clinical consequances of enzymes induction depend upon whether the drug acts as parent drug or metabolites. The increased rate of metabolism of the parent drug will result in decreased pharmacological effects and shortened duration of action. In case of action of liver enzymes on metabolites (as in cyclophosphamide), then increased effect

and toxicity will result from enzyme induction. These phenomina occurs in drugs metabolized by cytochrom P - 450 system such as corticosteroids, grisofulvin, digoxin , theophyline and coumarin .

Table (20): Interactions due to enzyme induction

Drug affected	Inducing agent (s)	Effect of interaction
Anticoagulants (oral)	Barbiturates Carbamnzcpine Dichlornlphcnazone Glutethimide Phennzone Rifampicin (rifampin)	Anticoagulant effects reduced
Contraceptives (oral)	Barbilurates Phenytoin Primidone Rifampicin Carbamazepine	Contraceptive effects reduced. Breakthrough bleeding, contraceptive failures
Corticosteroids	Aminoglutethimide Barbiturates Carbamnzepine Phenytoin Primidone Rifampicin	Corticosteroid effects reduced
Haloperidol	Tobacco smoke	Haioperidol effects reduced
Pentazocine	Tobacco smoke	Pevtazcine effects reduced
Phenytoin	Rifampicin (rifampin)	Pentazocin effects reduced. Seizure-risk increased ,
Theophylline	Barbiturates Rifamptcin Tobacco smoke	Theophylline effects reduced

2.1.3.2. Enzyme inhibition :-

Drugs that inhibit hepatic microsomal enzymes result in decrease metabolism of other drugs and consequently high blood level with subsequent symptoms of toxicity. These drugs include chloramphenicol, cimetadine, phenothiazines and organophosphate insecticides which prolong action of drugs that are normally inactivated by microsomal oxidation reactions e.g. barbiturates , digoxin and theophylline.

Table (21): Interactions due to enzyme inhibition:

Drug affected	Inhibiting agent (s)	Clinical outcome
Alcohol	Chlorpopamide Disulifram Latamoxef Metronidazole	Disulfiram-reaction due to rise in blood acetaldehyde levels
Anticoagulants (oral)	Metronidazole Phenylbutazone Sulphapyrazone	Anticoagulant effect increased. Bleeding possible
Azathioprine Mercaptopurine	Allopurinol	Azathioprine/mercaptopurine effects increased; toxicity
Caffeine	Enoxacin Idrocilamide	Caffeine effects increased. Intoxication possible
Corticosteroids	Erythromycin Triacetyl-oleandomycin	Corticosteroid effects increased. Toxicity possible.
Phenytoin	Chloramphenicol Isoniazid	Phenytoin effects increase. Intoxication possible
Suxamethonium	Ecothiophate	Neuromuscular blockade increased. Prolonged apnoea possible.
TolbuLamide Chloramphenicol	Azapropazone Phenylbutazone	Tolbutamide effects increased Hypoglycaemia possible
Tyramine-containing foodstuffs	Monoamine oxidase inhibitcrs (MAOI)	Tyramine-induced hypertensive crisis (other mechanisms also involved)

2.1 .3.3. Changes in blood flow through the liver :

Some drugs as cimitidine decrease hepatic blood flow and thereby increase the bioavailability of proanolol. Other drugs increase the flow of blood through the liver so that their metabolism is increased .

2.1.4. Interactions due to changes in excretion: -

a) Decreased active secretion:-

Many acidic drugs e.g. penicillins, cephalosporins, salicylates, probencid are actively secreted into urine by the renal tubular acid transport system . Competition for active transport between drugs may slow the rate of excretion. Prolonging penicillin blood levels by concomitant administration of probeneid is benificial

b) Increased passive excretion:-

* altering the urinary pH increases the excretion of ionizable drugs by iontraping, preventing their reabsorption from tubular urine.

(1) urinary alkalinizers (e.g. sodium bicarbonate) increase the excretion of acidic drugs as nalidixic acid, nitrofurantion, phenobarbitone and streptomycin

(2) Urinary acidifiers (e.g. ammonium chloride) increase the excretion of basic drugs as amphetamine and chloroquine .

** Increasing urine flow by diuretics hastens the excretion of many drugs through decreasing their reabsorplion from the nephron .

c) Changes in kidney blood flow:-

If the synthesis of prostaglandins is inhibited by indomethacin, the renal excretion of lithium is reduced and its serum levels rise as a result.

2.2 Pharmacodynamic interactions:-

2.2.1 Antagonistic or opposing interactions:-

2.2.1.1. Specific - receptor antagonists are available for certain receptor agonists. These antagonists are used therapeutically to block or reverse agonist activity; however antagonism may result in reduced efficacy e.g.

(a) antihistaminics have weak anticholinergic actions that reduce the effect of miotics in glucoma .

(b) phenothiazine tranqulizers have an α adrenergic blocking action that oppose the vasopressive action of epinephrine and produce hypotension .

2.2.1.2. Bacteriostatic antibiotics (e.g. tetracycline) slow bacterial growth; so these agents may antagonize the action of bacterial cell wall inhibitors (e.g. penicillins, cephalosporins), which are most effective against rapidly growing organisms.

2.2.2. Additive or synergistic interactions :-

It is observed with many classes of drugs, including hypnotics, sedatives, tranqulizers and the individual sulphonamides in triple sulphonamide preparations.

2.2.3. Synergistic effects:-

2.2.3.1. Therapeutic synergism: e.g. sulphonamide-trimethoprim combinations.

2.2.3.2. Potentiatlon of toxicity: e.g. combination of aminoglycoside and frusemide or tetracyclines and methoxyflurane (halogenated ether).

Drug-food interactions

Drug-food interactions may result in decreased drug efficacy or increased drug toxicity. The increasing complexity of drug therapy regimens has increased the potential for drug-food interactions to occur, reinforcing the need to develop methods to prevent clinically significant drug-food interactions.

Drug-food interactions may alter the effects of drugs by:

A- Interfering with pharmacokinetic processes such as

1- Absorption of drugs:

Food may influence drug absorption through:

a) Its action in slowing gastric emptying.

b) Binding with drugs, decreasing the access of drugs to sites of absorption.

c) Altering the dissolution rate of drugs.

d) Altering the pH pf gastrointestinal contents.

Examples:

* Absorption of tetracychines and ciprofloxacin decreased when taken with milk or other milk products as calcium can decrease absorption of drug.

* Absorption of digoxin is decreased after taking concurrently high fiber food.

* Absorption of vitamin K is decreased when administered with mineral oil. This leads to increase the effect of dicumarol and cocumarin.

* Absorption of penicillin V and quinolone derivatives as reduced in the presence of food (must given 1 hour before or 2 hours after meal).

2- Pencillin and erythromycin are inactivated in the stomach, when given with acidic foods:

3. Disturbance of excretion:

- Administration of foods with excessive sodium together with fruosemide and hydrochlorothiazide cause excessive loss of potassium and induce electrolyte disturbances.
- Administration of potassium- rich foods together with K-sparing diuretics as amiloride, triametrene and spironolactone cause retention of potassium and cardiac problems.
- Food may influence urinary pH values. The excretion of amphetmine is influenced by the type of diet. Balanced protein food provides acidic urine (average pH of 5.9). Amphetamine is execrated in acidic urine about 56% in the first 8 hours. Low protein diet which provides an alkaline urine (average pH of 7.6). Amphetamine is execrated in alkaline urine about 6% in the first 8 hours.

B- Interfering with pharmacodynamic effects:

e.g. interaction of warfarin sodium with leafy green vegetables, whereby hypoprothrombinemic effect of warfarin may be decreased and thromboembolic complications may develop.

Antineoplastic drugs decreased food intake and nutritional deficiency will occur, so special attention must be taken in consideration to prevent significant drug-food interactions.

XVII. CLINICAL PHARMACOLOGY

- **Definition**
- **Clinical cases**

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PROFESSOR OF PHARMACOLOGY

Def.: Clinical pharmacology is the application of pharmacologic principles for the treatment of animals. Controlled evaluation of the efficacy and safety of drug therapy in animal patients is also a major concern in clinical pharmacology.

Case No: 1

Fowl cholera

Chicken, 8 weeks old with yellowish brown diarrhea, comb and wattle become pale in colour .Birds are unable to stand , and blood sample revealed ***pasterulla multocida*** (Gm –ve) .

R/

Sulphaquinoxaline 20% (W.S.P)

1gm /L of drinking water for 3-5 days.

Group: Sulphonamide (Antimicrobial agent)

M.O.A:.due to the chemical similarity with PABA , bacteria takes sulphonamide instead of PABA ,so prevents the formation of folic acid which needed for bacterial growth

Uses: Treatment of fowl cholera in poultry.

> **R/**
>
> **Oxytetracycline 20% (W.S.P)**
>
> **1.5gm /L of drinking water for3- 5 days.**

Group: Tetracyclines (Broad spectrum antibiotic)

M.O.A: Inhibiting bacterial protein synthesis

Uses: Treatment of fowl cholera in poultry.

> **R/**
>
> **Vit AD3E 100.000 IU/ml (oral solution)**
>
> **25 ml / 100 liters of drinking water .**

* It is vitamin mixture including :-

(a) **Vit A** which is a growth factor and epithelial cells protective .

(b) **Vit D3** is essential for bone growth and precipitation of Ca-phosphate in bones .

(c) **Vit E** is antioxidant and essential for reproductive capacity .

Case No: 2

Hypoglycemia (Bovine ketosis)

Cow 400 kg b.wt. , 1 st week after parturition , emaciated, locomotor dysfunction ,body temperature is normal , ketone smell in the breath , milk and urine .

R/

Dextrose 50 % (inj.sol)

500 ml i.v.

* for correction of hypoglycemia by i.v. infusion .
* It is a source of glucose .

R/

Glycerol	**240 gm**
Warm water to	**1 liter**

M.FT.sol.

Sig : This amount , bid and then 120 gm daily for another 2days

* It is given orally as it is glycogenic agent .

R/

Molasses 1 liter diluted with warm water .

* It liberates the enteroglucagone from small intestine , which stimulate alfa cells of pancrease to secreate glucagone , which increases blood glucose level .

R/
Dexamethasone 10 ml/head . i.m.

* It is glucocorticoid agent ,which rises plasma glucose level .
* It stimulates gluconeogenesis (synthesis of glucose from A.As.)

Case No: 3

Pyelonephritis

Feverish Ram, 50kg body weight complaining from renal colic with scanty urine .X-ray revealed no calculi .Urine examination indicated gram –ve ***protus*** and ***pseudomonas*** infection.

(Advocin)®

R/

Danofloxacin 2.5 % (inj.sol)

2.5 mg/kg b.wt .i.m.for 3 days.

Group: Fluoroquinolones (Antimicrobial agent).

M.O.A: Inhibiting DNA gyrase enzyme.

Uses: Treatment of urinary tract infections caused by the causative organisms.

R/

Atropine sulphate 1%

1ml/100 kg b.wt. s/c or i.m.

Group: Parasympatholytics.

M.O.A: Muscarinic receptors blockers.

Uses: Treatment of renal colic (due to smooth muscle relaxation).

R/

Sulphafurazole 20%
Trimethoprim 4%
0.5 gm/1 lit.drinking water daily for 3-5 days.

Sulphafurazole

* It is effective on Gram –ve bacteria acting by competition with bacterial PABA depriving bacterial cells of the essential folic acid formation stopping its growth.

Trimethoprim

*Sulphonamide synergist with antibacterial activity.

It acting by :- inhibiting the folate reductase enzyme , so inhibiting the conversion of dihydrofolate to tetrahydrofolate rendering the bactericidal combination.

R/

K citrate	**1.00**
Am .chloride	**1.00**
Spiritus etheri nitrosi	**2.00**
Aqua ad	**1000.00**

MFT mixture
Sig : 5-10 ml orally daily for 3 days.

Diuretic mixture:

(a) **Pot. citrate** is an osmotic diuretic increasing urine osmolarity inducing diuresis .

(b) **Am. chloride** is an acidifying diuretic inhibiting Na/H exchange in the renal tubular cells leading to NaCl loss with water inducing diuresis. (c) **Sp . etheri nitrosie** is a smooth muscle relaxant releaving renal colicy pains .

R/
Ketoprofen 10% (inj.sol)
3 mg/kg b.wt. by IM injection daily for 3 days.

*It is analgesic antipyretic lowering the body temperature of feverish animal with mild sedation.

***It acts by**:-

(a) Antipyretic by affecting the thermoregulatory center in the hypothalamus producing heat loss by peripheral vasodilatation.

(b) Anti-inflammatory and analgesic by inhibiting prostaglandin synthesis and release.

Case No: 4

Milk fever (Hypocalcemia)

Cow,350 kg B.wt. , second day after parturition , sternal recumbancy and the head turned into the flank , dry muzzle and hypothermia .

R/

Calcium borogluconate	**14.8 mg/ml**
Mag.hypophosphite	**4.6 mg/ml**
Dextrose	**200 mg/ml**

400 ml . i.v. and 200 ml by s/c as maintenance dose

*it is a source of calcium supplementation which needed for neuromuscular function.

R/

Dexamethasone 2 mg/ml

1 ml/25 kg.b.wt. by IM injection.

* As corticosteroid drug which .ncrease blood glucose level so raises the body temperature and warm the animal.

R/

Vitamin AD3E 10 ml . i.m.

* Single dose of vitamins to mobilize the stored calcium from the bones.

Case No: 5

Blood parasite (Babesiosis)

Buffalo bull 350 kg body weight ,with body temperature 41.5 c , off food , anaroxia ,dry muzzle ,blood sample revealed ***Babesia bovis*** ,profuse lacrimation is present .

R/

Oxytetracycline inj . 10%

1 ml/10 kg . B.wt .i.m. for 5 days.

Group: Tetracyclines (Broad spectrum antibiotic)

M.O.A: Inhibiting bacterial protein synthesis

Uses: Treatment of erythrocytic form of babesia.

(Berenil)®

R/

Diminazine aceturate 7%

3.5 mg/kg b.et. by IM given once.

Group: Antibabesial drug.

M.O.A: Interfer with DNA synthesis.

Uses: Treatment of babesiosis.

(Imisol)®

R/

Imidocarb dipropionat 12 %

1.2 mg/kg .b.wt. once s.c.

Group: Antibabesial drug.

M.O.A: Interfer with DNA synthesis.

Uses: Treatment of babesiosis.

R/

Na-salicylate 25 gm orally.

*It is analgesic antipyretic lowering the body temperature of feverish animal with mild sedation .

***It acts by** :-

(a) Antipyretic by suppresing the thermoregulatory center in the hypothalamus producing heat loss by peripheral vasodilatation.

(b) Anti-inflammatory and analgesic by inhibiting prostaglandin synthesis and release.

Case No: 6

Retained placenta

Buffaloe cow 350 kg body weight , post partrum heamorrage , retained placenta , metritis (G+ve and –ve organisms) , fever , abdominal pains , developing milk fever .

R/		
	Stilboestrol dipropionate	**20 mg i.m.**
	Syntocinon	**30 mg i.m.**

Syntocinon

A synthetic oxytocin for sensitization of the uterine wall for the ecbolic effect of stilboestrol to get rid of the placenta .ItContracts themyometrium and help the let down of milk by contracting the milk acini of the mammary gland.

Stilboestrol dipropionate

* A synthetic eostrogen stimulating the presensitised myometrium by oxytocin for the expulsion of the retained placanta

(Methergin)®

R/

Methyl ergometrine 10 mg/kg.b.wt i.m.

* An ergot alkaloid specifically contracting the myometrium helping its rapid involution and contracting the bleeding blood vessels after the expulsion of the featus , fetal membranes and placenta , checking post partum heamorrage.

R/

Acriflavine 0.01% sol for uterine wash .

* An acridine antiseptic dye acting by inhibiting the synthetic processes of microorganisms by intercelating with DNA . It is safe to be used internally as a uterine wash after expulsion of the retained placenta .

R/

Atropine sulphate 1%

1ml/100 kg b.wt. i.m.

* An anticholenergic belladonna alkaloid relaxing the smooth muscles releaving colicy pains accompanying metritis and retained placenta.

R/

Oxytetracycline Hcl (500 mg tablets

(2 tab.intrauterine daily for 3 days)

* A broad spectrum antibiotic acting by inhibiting the bacterial protein synthesis .It is applied locally for its bacteriostatic effects on G+ve and G-ve organisms inducing metritis .

R/

Oxytetracycline Hcl 10 % 1 ml/10 kg b.wt. i.m. daily for 5 days .

Group: Tetracyclines (Broad spectrum antibiotic)

M.O.A: Inhibiting bacterial protein synthesis

Uses: Treatment of meteritis.

R/

Ca borogluconate 20% 500 ml for i.v. infusion to be repeated till releave of symptoms of milk fever .

* A calcium gluconate salt with boric acid acting as a replacement therapy for the sudden drop in the calcium level of the heavy milking buffaloe cow after delivery and exhaustion of calcium resources by bony development of the featus . It gives a prompt releave of symptoms .

Case No: 7

Organophosphorus toxicity

Buffaloe bull 350 kg body weight , history of exposure to an organophosphorus insecticide . secretions , bradycardia , hypotension ,bronchial asthma, excitement and paralysis of the hind limbs .

R/

Atropine sulphate 1% 1 ml/100kg b.wt. s/c to be repeated till atropinezation.

Group: Parasympatholytics.

M.O.A: Muscarinic receptors blockers.

Uses: Treatment of bradycardia and bronchial asthma.

(Toxogenin)®

R/

Pralidoxime (P-2.A.M.) 10 ml i.m.

Group: Anticholine estrase reactivator.

Action&MOA: by de-phosphorylation of the enzyme from the org.ph .insecticide – thus the choline estrase enzyme become free to hydrolyse the AC.ch

R/

Mg so4 500.00

Aqua ad 1000.00

MFT sol .

Sig : one drench

* A saline purgative by increasing osmotic tension as not absorbed and collect water in the intestine increasing the bulk and stimulating peristalsis which help for the expulsion of the included Organophosphate not yet absorbed .

R/

Furosemide (Dimazon)®

0.5-1 mg/kg by IV twice daily for 3-5 days.

Group:Loop diuretics.

Action &MOA: inhibiting the reabsorption of sodium and chloride in the ascending limb of loop of henel, Inhibition of sodium chloride reabsorption is followed by hypokalemia as the high concentration of NaCl in the distal tubules attracts out potassium ions. They tend to increase Ca and Mg secretion and retention of uric acid in blood and rising up the blood sugar level.

R/

Pentobarbitone Na 20%

120-200 mg/kg.b.wt.by IV.

Group: short acting barbiturate

Action &MOA: Non specific anticonvulsant by preventing the conversion of pyruvate to acetate,resulting in inhibition of AC choline formation.

Uses: Relief of convulsion and excitation.

Case No: 8

Calf-Scour

Calf weighting 100 kg ,feverish suffering from severe diarrhea , colic and dehydration . Fecal examination revealed G-ve ***E.coli*** and ***salmonella***.

R/
Oxytetracycline
a\a\ 5 %   Neomycin
Sig: 1 gm/10 kg .b.wt. given orally twice daily for 3-5 days.

Oxytetracycline

Group: Tetracyclines (Broad spectrum antibiotic)

M.O.A: Inhibiting bacterial protein synthesis

Uses: Treatment of diarrhea caused by G – ve bacteria.

Neomycin

Aminoglycosides(bacteriostatic antibiotic). **Group**

M.O.A: Inhibiting bacterial protein synthesis

Uses: Treatment of diarrhea caused by *E.coli-salmonella*

R/
Ketoprofen 10% (inj.sol)
3 mg/kg b.wt. by IM injection daily for 3 days.

*It is analgesic antipyretic lowering the body temperature of feverish animal with mild sedation .

***It acts by** :-

(a) Antipyretic by suppresing the thermoregulatory center in the hypothalamus producing heat loss by peripheral vasodilatation.

(b) Anti-inflammatory and analgesic by inhibiting prostaglandin synthesis and release.

R/

Atropine sulphate 1% 1ml/100 kg b.wt. s/c or i.m.

Group: Parasympatholytics.

M.O.A: Muscarinic receptors blockers.

Uses: Treatment of colic (due to smooth muscle relaxation).

R/

Na cl	**5.5**
Ca cl_2	**0.3**
Mg cl_2	**0.3**
Na acetate	**6.1**
K acetate	**1.0**
Aqua dist . add	**1000.00**

MFT injec .

Sig : 250 ml by i.v. then given by s/c twice daily.

Replacement fluid:

* Nacl , $Cacl_2$, $Mgcl_2$, Na acetate and K acetate are electrolytes compensating those lost with watery diarrhea and dist.water correcting dehydration and plasma concentration .

Case No: 9

Avian coccidiosis and clostridial infections

Chickens 21 days old, bloody diarrhea and lab.examination showed *Eimeria tenella* , *E.acervulina* and *clostridia perfringens (type A).*

(Baycox)®

R/

Toltrazuril 2.5%

3 ml/1 liter drinking water for 8 hours daily for 2 successive days.

Toltrazuril:

Group:Anti-Coccidial

MOA:Interfering with nuclear division of schizont and prevent differentiation into : (micro / macro gametocytes)

Uses:Treatment of cecal and intestinal coccidiosis in chickens and turkeys .

Cox . Mix® . Powder

R/

sulphadimidine sod	**15%**
Amprolium Hcl	**12.5%**
Ethopabate	**0.8%**
Vit K3	**2%**

1 gm /1lit drinking water daily for 5-7 days.

Sulphadimidine

Group:sulphonamide .

MOA: Competitive antagonism with PABA in the coccidial **cell** , so preventing the formation of folic acid .

Uses :coccidiosis in chickens – turkeys

Diaveridine :

Group:coccidiostate

MOA:prevent conversion of dihydrofolate to tetrahydrofolate by **inhibition** of dihydrofolate reductase enzyme → prevent formation of folic acid

Uses: coccidiosis in chicken – turkeys .

Amprolium :

Group :anticoccidial agent

MOA:pevent utilization of thiamin (Vit B1) by **Eimeria** species(antithiamine)

Uses: coccidiosis in chicken – turkeys.

Ethopabate:

Group: anticoccidial agent.

MOA:PABA antagonist

Uses: coccidiosis in chicken – turkeys.

Vit K3:

Fat soluble vitamin is essential for blood clotting. It is helpful in protection against ceacal bleeding due to coccidiosis .

(lincol)® oral powder

R/

Lincomycin HCE 40%.

0.5 –1 gm / 1lit drinking water ultrinatively with anticoccidial product daily for 5 days.

Lincomycin:

Group: bacteriostatic antibiotic from lincosamide group.

MOA: inhibiting bacterial protein synthesis by binding to 50 s ribosomal subunit

Uses: treatment of clostridial infection (G+ve bacteria) .

Case No: 10

Avian CRD

Turkey flock of 38 days old , clinical signs showed respiratory symptoms of CRD with whitish exudate and lab examination showed Mycoplusma gallisepticum , M.meleagridis and E.coli infections.

Mycomas ® oral sol
R/
Norfloxacin 20%
0.5 ml / 1 lit 1 drinking water daily for 3-5days.

Nor floxacin:

Group: Fluroquinolones (antimicrobial)

MOA: Inhibiting bacterial DNA gyrase enzyme .

Uses: CRD ,and air saccuilits in chikens – turkeys.

Pulmotil ® oral sol
R/
Tilmicosin 25%
0.5-1ml / 1lit drinking water daily for 3-5days.

Tilmicosin:

Group: promacrolide antibiotic

MOA: Inhibiting bacterial protein synthesis by binding with 50 s ribosome of the organism.

Uses: Mycoplasma , G+ve and G-ve bacterial infection

Bisolvon ®

R/

Bromohexine HCl 1%

1gm / 1lit drinking water daily for 3-5days.

Bromohexine HCL:

Group: Mucolytic drug.

MOA: increasing lysosomal enzyme activity .

Uses: bronchitis associated with mucous plug.

Case No: 11

Endo and Ectoparasitic infestation

A camel of 500 kg b.wt, emaciated , pale eye,itching in the neck and shoulder region and skin scrapping showing mites.Faecal exam. revealed eggs of *Fasciola gigentica.*

Iver-plus ®
R/

Ivermectin	**1gm**
Clorosulon	**10 gm**
Exip Q,S	**100ml**

(1ml of injectable solution/ 50kg b.wt by s/c)

Ivermectin:

Group: broad spectrum antinematodal and ectoparasiticide.

MOA: causing paralysis of parasites through ↑ the release of GABA from neuromuscular junction →prevent transmission of stimuli → No contraction of Ms → paralysis →death.

Uses: antinematodal durg against GI nematodes & lung worm & lice , warble and mange(treatment of external& internal parasites).

Clorsulon

Group: Fasciolicide

MOA:it kills the worm by inhibiting the process of glycolysis , so inhibit energy production .

Uses: treatment of mature and young liver flukes.

Case No: 12

Mastitis

A cow 400kg b.wt 3 months after calving suffered from acute mastitis, painful udder with inflammtion, colisepticaemia and lab diagnosis revealed *staph. Spp*, *pseudomonas aeruginosa* and *E.coli*

Mastilex® Intramammary infusion	
R/	
cephalexin	**350 mg**
Gentamycin sulphate	**35 mg**
Exip Q.S	**10 ml syringes**
One syringe per quarter dialy for 3-5 days	

Cephalexin:

Group: Cephalosporins (bactericidal antibiotic)

MOA: Inhibit bacterial cell wall formation

Uses: treatment of mastitis due to Gram+ve bacteria and G –ve bacteria especially those penicillinase producing organisms.

***Gentamycin*:**

Group: Aminoglycosides (bacteriocidal antibiotic)

MOA: Inhibit bacterial protein synthesis by binding with 30s ribosomal units.

Uses: treatment of mastitis due to G-ve bacteria.

Tri-complex ® injection

R/

oxytetracyline HCL	**100mg**
Dexamethasono sod .phosphate	**2mg**
Diphenhydramine Hcl	**20 mg**
Exip .Q.S	**1ml**

1ml/10 kg.b.wt. by IM once daily for 3-5 days.

Oxytetracycline:

Group: Tetracyclines (bacteriostatic antibiotic).

MOA:Inhibiting bacterial protein synthesis by binding with 30 s ribosomes.

Uses: Treatment of mastitis caused by G – ve &G +ve organisms.

Dexamethasone:

Group:Synthetic corticosteroid.

MOA: Inhibiting phospholipase enzyme→ inhibiting prostaglandin synthesis.

Uses: Inflammatory conditions.

Diphenhydramine:

Group:Antihistaminic.

MOA:H 1 blockers.

Uses:Allergic conditions.

XVIII. DRUG TOXICOLOGY

- **Background**
- **Classification**
- **Treatment**

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LECTURER OF PHARMACOLOGY

Drug Toxicology

Background

- Toxicology is the study of the harmful effects of chemical compounds on biologic system, including their actions, effects, how to avoid their harmful effects and how to deal with the poisoned cases.
- Toxin is the poison produced from a biologic source (eg venoms, bacterial toxins and plant toxins), while as toxicosis, poisoning and intoxication different names for disease produced by a toxin.
- Source of a poison (accidental ingestion of poisons in animals is common)
  1. Many insecticides and nematocides contain sugar to enhance their job as baits.
  2. Some poisons are naturally sweat in taste (eg lead salts and ethylene glycol).
  3. Poisonous plants are major source of toxication in large animals
  4. Improper use of chemicals as pesticides, herbicides or fertilizer may result in accidental poisoning of grazing animals.
- Poisoning is a medical emergency that requires rapid treatment to separate between the life and death.

- Specific antidote is available for only few poisons and nonspecific antidote is essential for most of the poisons.

Fate of the poison in the body:

- First the poison enters the animal body either by skin absorption or after oral ingestion.
- Some of the poison is not absorbed and some is absorbed and circulate in to the liver.
- In the liver it could get metabolized to its inactive form or more serious form or it could be stored in the body.
- Some of the poisons get excreted by the kidneys, salivary glands, sweat glands or in the expiratory air.
- To deal with a particular case of poisoning we need to know its fate in the body so we can be able to either avoid its harm or at least decrease it to save the animal life.
- Levels or types of poisoning effects:
  1. Acute poisoning: in which acute symptoms show off after getting a single large dose of the poison. The symptoms could by digestive like vomiting, diarrhea and salivation or could be nervous like excitement, tremors, convulsion, paralysis and coma.
  2. Subacute poisoning: the same as acute one but with smaller dose, less sever symptoms and less rapid onset.
  3. Chronic poisoning: results from accumulated effect of a drug as the dose is too small to show prominent symptoms (remember the chronic use of OP leads to demyelination of the peripheral nerves that leads to nerve damage and finally paralysis.

Factors affecting the severity of the poison:

- Factors related to the **poison:**

1. Amount of the chemical (large amount is more toxic).
2. Form of the chemical (liquid form is more toxic)
3. Solubility of the chemicals (soluble chemical is more toxic).
4. Route of administration (parenteral route produce faster effect).
5. Accumulation of the drug (cumulative chemicals predispose toxicity).

- Factors related to the **animal:**
  1. Species of the animal (cats are very sensitive to the phenacetin, paracetamol and OP) .
  2. Age and health condition of the animal.
  3. Conditions of the stomach: empty stomach expedite the effect.
  4. Kind of food in the stomach: high fat ingesta increase the solubility of the lipid soluble chemicals and increase their toxic effects (as canthridine and OP).
  5. Idiosycracy: some individuals severely respond to particular chemicals so if they get in contact with a dose that is just little bigger than the therapeutic one may get to toxicity.
  6. Addiction and habituation: that my decrease the severity of toxicity.

Symptoms of poisoning on the animal: the poisoned animal could show one or more of the following groups of symptoms

- **Sudden death:** as cyanide, strychnine, CO2, CO, ether, phenol and chloral hydrate in large doses.
- **Eye:**
  - **Miosis:** poisonous mushroom, nicotine in the first stage, and morphine.

- Mydriasis: atropine, belladonns, nitrates and last stage of nicotine tox.

- **Odor of the breath**: ammonia, acetone, camphor, ether, cresole and iodine.
- **Mouth:**
    - **Dry mouth:** atropine and belladona
    - **Drawling:** OP, ammonia, arsenic, mercury and iodine.
- **Skin and mucus membrane:**
    - **Dry skin**: alcohol and nicotine
    - **Rashes:**
        - Arsenic causes eczema.
        - Belladonna cause scarlet rash
        - Chloral hydrate causes urticaria.
    - **Cyanosis of the MM**: as aniline dyes and phenacetin.
    - **Skin and MM corrosion:** as glacial acetic acid, strong acids, formaldehyde, trichloroacetic acid, NaCl and KCl.
    - **Excessive sweating:** as pilocarpine and pot. iodide.
- **GIT disturbances** (nausea, vomiting and diarrhea) as most strong acids and alkalies, ergot alkaloids, digitals, phosphorous compounds and lead compounds.
- **Delirium:** alcohol, atropine, camphor and stramonium.
- **Stupor (day dreaming):** barbiturates, bromide, chloral hydrate and chloroform.

Classification of poisons:

- A. According to the **source:**
    - **Organic:**
        - Animal source: snake venoms and canthridins.
        - Plant source: atropine, strychnine and digitalis
        - Synthetic source: carbon tetrachloride
    - **Inorganic:**
        - Acids: HCl, H_2SO_4, carbolic acids and acetic acid.
        - Alkalies: NaOH, KOH, and NH_4OH.
        - Salts of metals: lead salts, mercury salts and cupper sulphate.
        - Salts of non metal elements: iodine and bromide salts
- B. According to the **degree of toxicity**:
    - **Strong poison**: severe symptoms and usually causes death, like arsenic and cyanide salts.
    - **Weak poison:** with less violent symptoms and usually does not lead to death, like alcohols.
- C. According to the **distribution of the effect:**
    - Local: as the irritant corrosive effect of acids and alkalis when come in contact with the animal skin.
    - Systemic: as the poison produces its effect systemically after its absorption from the site of application like arsenic, atropine, morphine and digitalis.
    - Mixed: some poisons produce local effect at the site of contact with the animal body and produce general effect after its absorption like the tarter emetic.
- D. According to the **system affected**:
    - CNS: depressant like morphine and stimulant like strychnine

- ANS: atropine and methacholine.
- CVS: digitoxin and strophanthin.
- Urinary: sulphanilamide and cantheridin.
- Respiratory: CO_2 and morphine.

- E. According to the **kind of effect** the poison produces:
  - Corrosives: strong acids and alkalis cause abrasions and ulcers in the skin and MM.
  - Narcotics: causing sleeping like barbiturates.
  - Stimulants: like stimulation of the brain by caffeine and SC by strychnine.
  - Depressants: like morphine on the brain, potassium bromide on the spinal cord and atropine on the parasympathetic system.

Diagnosis of poisoning

- Circumstances of the accident.
- Finding some of the poisonous plant or chemical at the scene of the accident or in the animal stomach.
- Watching the symptoms and their progress on the animal.
- Smelling the odor of the animal breath as the acetone or any other organic solvent poisoning.
- Color of the urine change to red in case of phenothiazine and to green in case of phenol poisoning.

General strategy of poisoning treatment

- **Inhibition of absorption:**
  - **Stomach lavage:** is done as early as possible while the poison is still in the stomach. Do not use in case of corrosives. It can be used

even at late time in case of morphine and arsenic poisoning (they are excreted in the stomach).

  - **Emesis:** by giving an emetic in the vomiting animals like conc. sodium chloride and copper sulphate or centrally by using apomorphine.
    - Do not use apomorphine in case of CNS depressant.
    - Do not use emetics in case of corrosives you may perforate the esophagus or the stomach.
    - Do not use in case of the poisons that anaesthetize the stomach like the carbolic acid (phenol).

- **Enhancing the excretion**: increase the rate of excretion through the bowel, kidney or skin
    - Using purgatives like laxatives or in case of horse it is good to give cholinergic stimulant like arecoline and pilocarpine.
    - Using diuretics as extra fluid infusion, caffeine or even strong diuretic like flrosemide.
    - Changing the urine pH to favor the excretion of the poison:
      - In case of acidic drugs like sulphonamides they are ionized in an alkaline pH so we can trap them in the alkaline urine by using NaHCO3
      - In case of alkaline drugs like amphetamine is ionized and get trapped in the acidic urine so use ammonium chloride to lower the urine pH.
    - Using diaphoretics like pilocarpine for dogs in case of poisoning with chemicals excreted in the sweat (potassium iodide is excreted in the sweat).

- Peritoneal dialysis in small animals by injecting physiological ringers solution intraperitoneally and remove it after 30 minutes and repeat it as required.

- **Supportive medicine:**
    - Maintenance of the cardiovascular function:
        - IV of physiological fluids or plasma if in case of shock.
        - Administration of glucocorticoids to help tissue perfusion.
    - Maintenance of the respiratory function:
        - Mechanical ventilation and may be endotracheal intubation.
        - High oxygen chamber in of case gases suffocation in small animals.
    - Maintenance of body temperature in case of comatosed or sedated animals by using hot pads, blankets or heating lamps.
- **Administration of antidote**:
    - **Symptomatic antidote** to prevent the general symptoms to appear on the animals:
        - Antiemetics in vomiting.
        - Astringents in diarrhea.
        - Stimulants in depression.
        - Artificial respiration in collapse.
        - CNS depressant in case of excitement, convulsion and sedation.
    - **Universal antidote:** 2 parts activated charcoal powder, one part tannic acid and one part magnesium oxide. Take 15 gm in a half a gallon of worm water.

- **Chemical antidote** by chemical precipitation, neutralization or decomposition (like starch for iodine, lemon juice for strong alkali and dilute ammonia water for strong acids).
- **Pharmacological antidotes** to counteract the pharmacological effect of the poison (atropine for physostigmine and barbiturates for strychnine).
- **Specific antidote** as mephnisine in case of strychnine, nalorphine in case of morphine and 2-PAM in case of OP.
- **Mechanical antidote**
  - **Entanglers:** as cotton ball and high fiber ration in case of sharp objects.
  - **Magnetic bar** is used to keep a nail in the reticulum of the cattle to avoid reticulo-pericarditis when a cattle swallow a nail.
  - **Charcoal** adsorbs poisonous gases on its surface in the intestine and getting it out with the feces without absorption.
  - **Chelating agents:** are materials that bind with the poisons and form inactive poorly dissociating complexes known as chelats.
    - **Dimercaprol**, British Anti Lewisite (BAL) provides 2 –SH groups to bind to the heavy metals (arsenic, mercury and cadmium) and make the –SH containing enzymes free from the metals.
    - **Penicillamine** (dimethyl cysteine) to chelate copper, mercury, zinc and lead.

- **Sodium calcium edetate** (EDTA): used in case of lead poisoning and chelating the radioactive metals, uranium and plutonium.
- **Desferrioxamine:** for the **ferric iron** *and* **sodium ferrocyanide for ferrous iron.**

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